

Manual of Operations  
For  
Therapeutic Clinical Trials

Clinical Research Management Branch (CRMB)  
Therapeutics Research Program

Division of AIDS  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Bethesda, Maryland

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## A. INTRODUCTION

Welcome to the Division of AIDS (DAIDS).

The DAIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), is the sponsor for these clinical trials. The Clinical Research Management Branch (CRMB), Therapeutics Research Program (TRP), DAIDS, is available to help your clinical site/center successfully conduct these trials. CRMB's role includes:

- Managing a comprehensive portfolio of grants, cooperative agreements, and contracts to implement all aspects of clinical trials research;
- Helping site staff understand their responsibilities for ensuring that the research is of high quality and conducted in accordance with all applicable regulations and guidelines;
- Developing procedures for the management of clinical sites/centers.
- Providing each clinical trials program with resources for developing study protocols, coordinating program-wide communication, and monitoring the performance of individual sites and the program as a whole; and identifying factors negatively affecting program performance and addressing these problems in collaboration with the program's leadership.

This reference manual is designed to provide your site/center with the information necessary to administer your clinical trials programs. It first explains the procedures that staff shall follow to establish clinical sites and pharmacies, and to ensure the quality of their study data. Next, an overview of the site monitoring process is provided. Following this, working instructions are presented regarding enrolling prisoners as volunteers, closing sites/centers, storing clinical trials records, and providing informed consent, etc. A listing of CRMB staff to contact for further information is also presented.

Be sure to check the Web page for your collaborative group to obtain additional information on group policies, procedures, organization, and resources.

If you have any questions or comments about this reference manual, please contact:

Clinical Research Management Branch  
TRP/DAIDS/NIAID/NIH  
6700-B Rockledge Drive, MSC 7624  
Bethesda, Maryland 20892  
(301) 496-8124

## **B. DAIDS/TRP/CRMB MISSION**

### **B.1. Division of AIDS**

The mission of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), is to increase basic knowledge of the pathogenesis, natural history and transmission of the Human Immunodeficiency Virus (HIV), and to promote progress in its detection, treatment, and prevention.

The DAIDS accomplishes its mission by planning, funding, implementing and evaluating grants, cooperative agreements, and contracts in the following areas: 1) basic and clinical research; 2) discovery and development of therapies for HIV infection and its complications; 3) discovery and development of vaccines and other preventive interventions; and 4) training of researchers.

### **B.2. Therapeutics Research Program**

The Therapeutics Research Program (TRP) of the DAIDS has responsibility for oversight and evaluation of the DAIDS-funded therapeutic clinical trials research programs. These programs include multiprotocol, multicenter cooperative groups performing clinical trials in adults and children, single-protocol cooperative groups, and single-site trials. They take place at hundreds of clinical sites/centers throughout the United States and in other countries. The TRP also has responsibility for oversight and evaluation of programs for drug discovery and pre-clinical evaluation.

The TRP identifies scientific priorities and needs, and develops new initiatives, including: 1) access to clinical trials for under-served populations which address the changing demographics of HIV disease, and 2) the research needs identified in consultation with voluntary and professional health organizations, including community-based organizations and health care providers. Working with other Government agencies and other components of the NIH, the TRP identifies the need for and prepares training initiatives specifically required for HIV therapeutic clinical trials efforts and coordinates the DAIDS research efforts regarding special population groups. The TRP evaluates operations of the clinical trials sites/centers, makes recommendations and provides assistance as necessary.

### **B.3. Clinical Research Management Branch**

The Clinical Research Management Branch (CRMB) of the TRP develops, implements, and evaluates a program of research grants, cooperative agreements, and contracts to conduct HIV therapeutic clinical trials. The program components include clinical sites/centers, as well as statistical and data management centers, a site monitoring contractor, and operations centers to develop study protocols and provide logistical support to clinical trial investigators. The CRMB also manages the fiscal resources supporting these programs.

As necessary, to ensure the successful completion of the research agenda, CRMB staff coordinate the efforts of clinical trials investigators, other DAIDS components (e.g., Pharmaceutical Affairs Branch, Regulatory Affairs Branch), other components of the NIH (e.g., other Institutes, Fogarty International Center), and other Government agencies concerned with HIV therapeutics clinical research.

Structure, Oversight  
and  
Financial Support  
of the  
Therapeutic AIDS  
Clinical Trials Groups

# Executive Branch of the Federal Government

## Cabinet

- Department of Agriculture
- Department of Commerce
- Department of Defense
- Department of Education
- Department of Energy
- **Department of Health and Human Services**
- Department of Housing and Urban Development
- Department of Interior
- Department of Justice
- Department of Labor
- Department of State
- Department of Transportation
- Department of Treasury
- Department of Veterans Affairs

# Department of Health & Human Services (DHHS)

## Major Organizations

- Administration on Aging (AoA)
- Administration for Children and Families (ACF)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- **Centers for Disease Control and Prevention (CDC)**
- **Health Care Financing Administration (HCFA)**
- Agency for Health Care Policy and Research (AHCPR)
- **Food and Drug Administration (FDA)**
- **Health Resources and Services Administration (HRSA)**
- Indian Health Service (IHS)
- **National Institutes of Health (NIH)**
- **Office for Human Research Protections\* (OHRP)**  
*Formerly the Office for Protection from Research Risks (OPRR)*
- Substance Abuse and Mental Health Services Administration (SAMHSA)

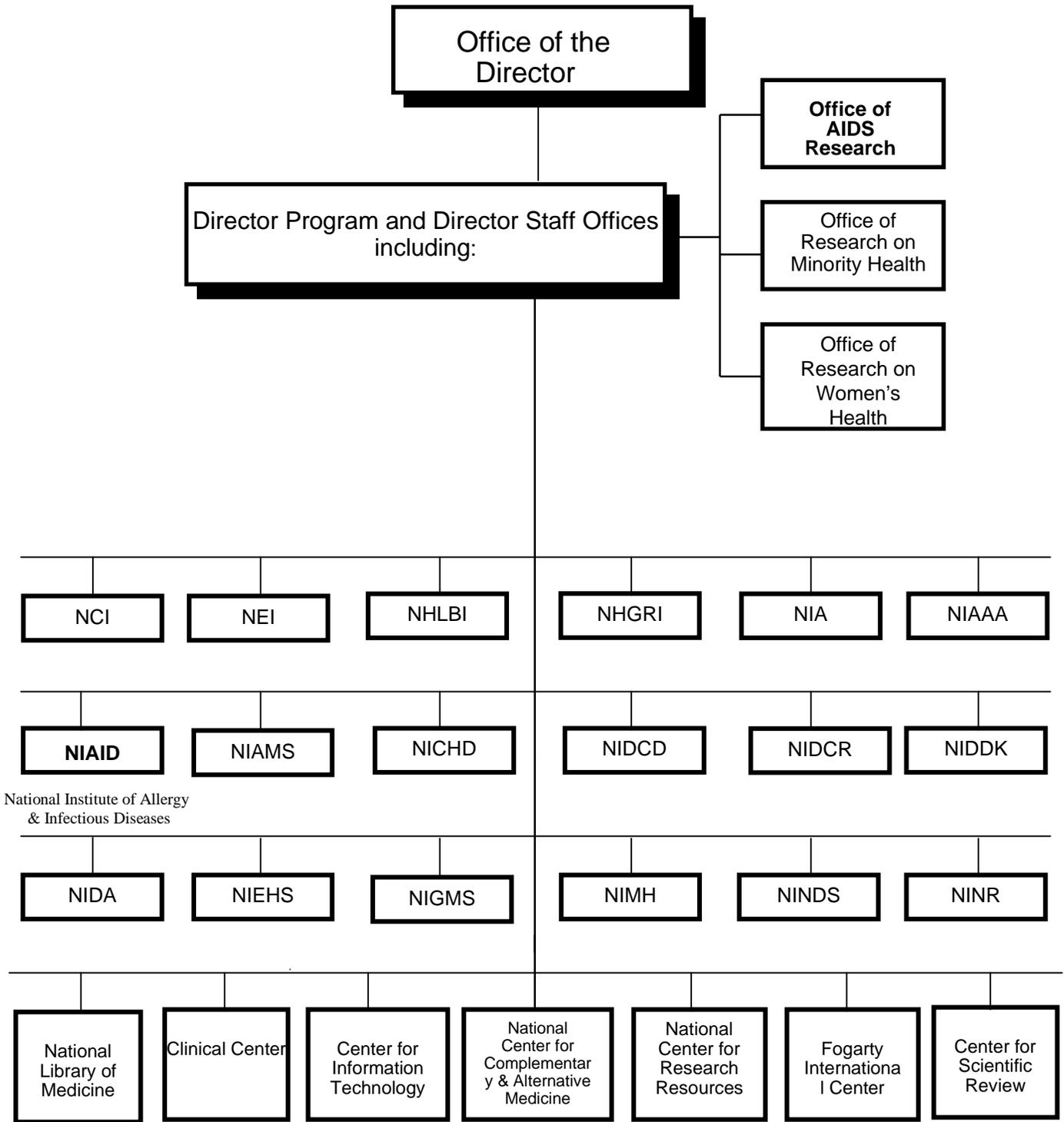
# Office for Human Research Protections (OHRP)

Responsible for developing and implementing all regulations (45CFR46), policies, and procedures related to the **protection of human subjects in research** conducted or supported by DHHS.

Includes requirements for:

1. Informed consent
2. IRB
3. Participation of special populations  
(e.g., pregnant women, fetuses, children, and prisoners)

# National Institutes of Health (NIH)

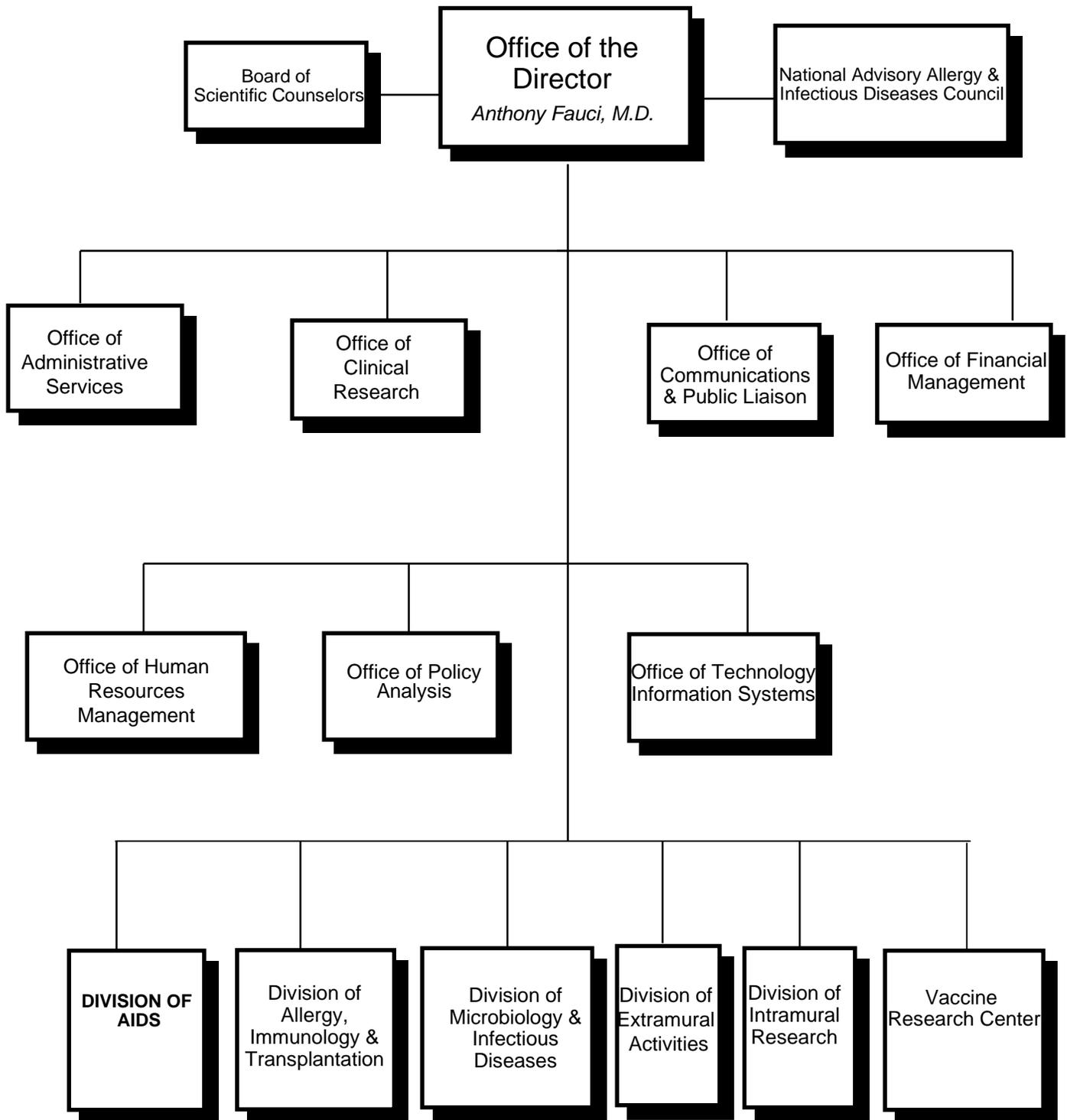


# Office of AIDS Research (OAR)

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- Responsible for the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program.
- Authority to plan, coordinate, evaluate and fund all NIH AIDS research.
- Responsible for developing annually, a comprehensive plan and budget for all NIH AIDS research.

# National Institute of Allergy & Infectious Diseases (NIAID)



# Division of AIDS (DAIDS)

## Office of the Director

Director, J. Killen, M..D.  
Deputy Director  
Vacant

## Office of Scientific Coordination

Director, P. Sager, Ph.D.

## Office of Program Operations and Scientific Information

Associate Director  
T. LaSalvia, M.P.H.

## Pharmaceutical Affairs Branch

Chief, A. Martinez, R.Ph

## Regulatory Affairs Branch

Chief, M. Luzar, Ph.D.

## Biostatistics Research Branch

Chief, D. Dixon, Ph.D.

## Therapeutics Research Program

Associate Director  
W. Duncan, Ph.D.

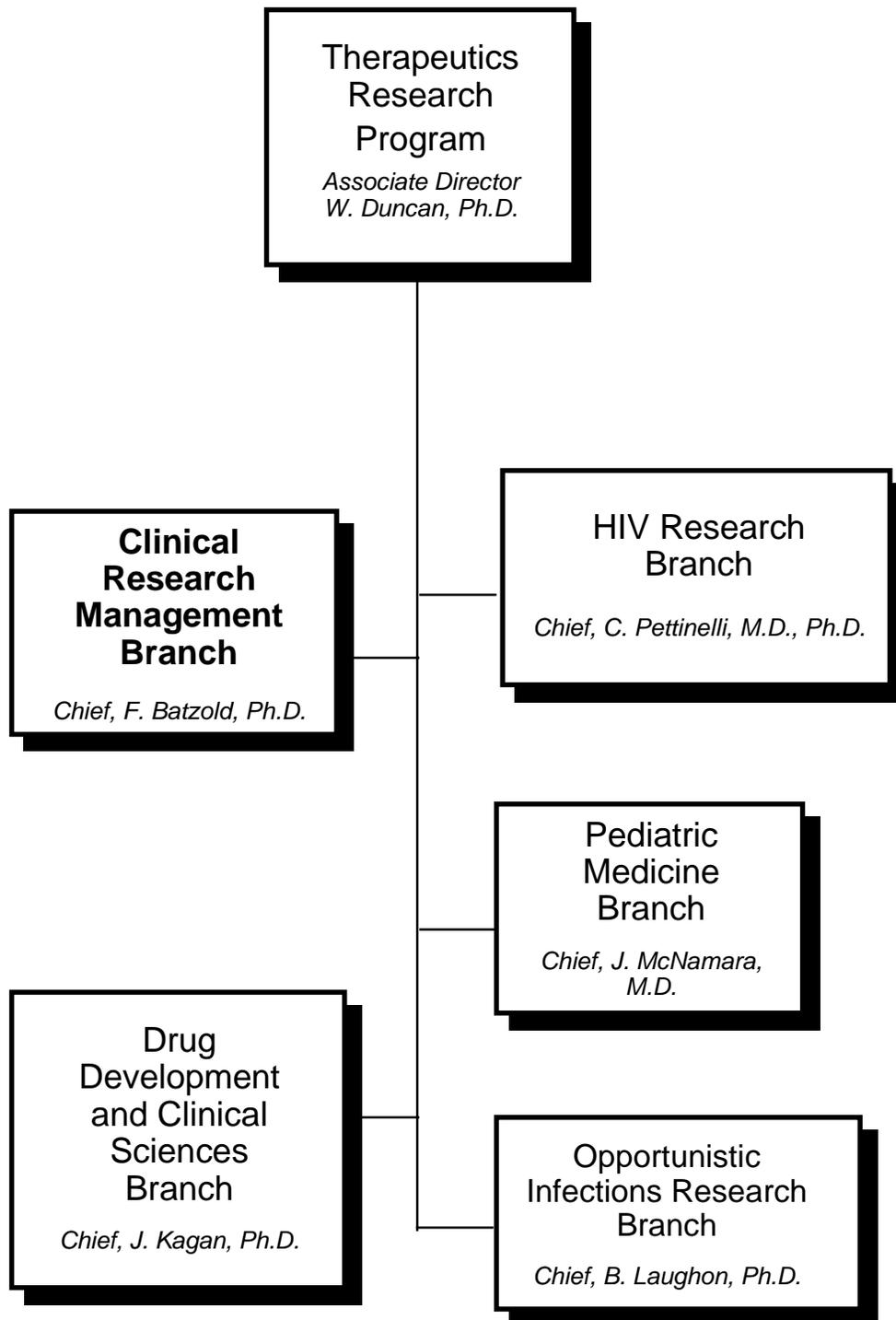
## Basic Sciences Program

Associate Director  
C. Dieffenbach, Ph.D.

## Vaccine and Prevention Research Program

Associate Director  
M. Johnston, Ph.D.

# Therapeutics Research Program (TRP)

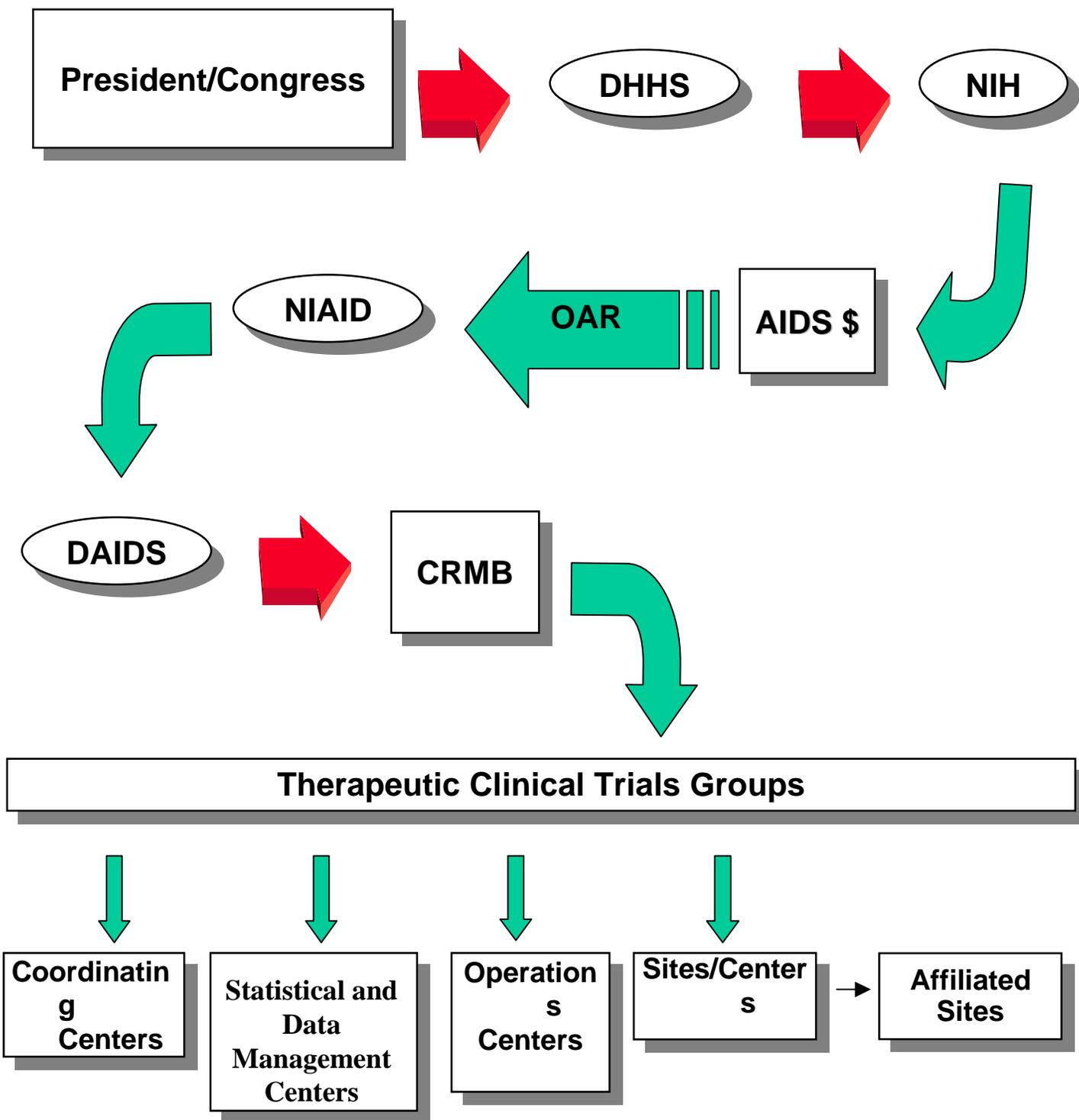


# TRP

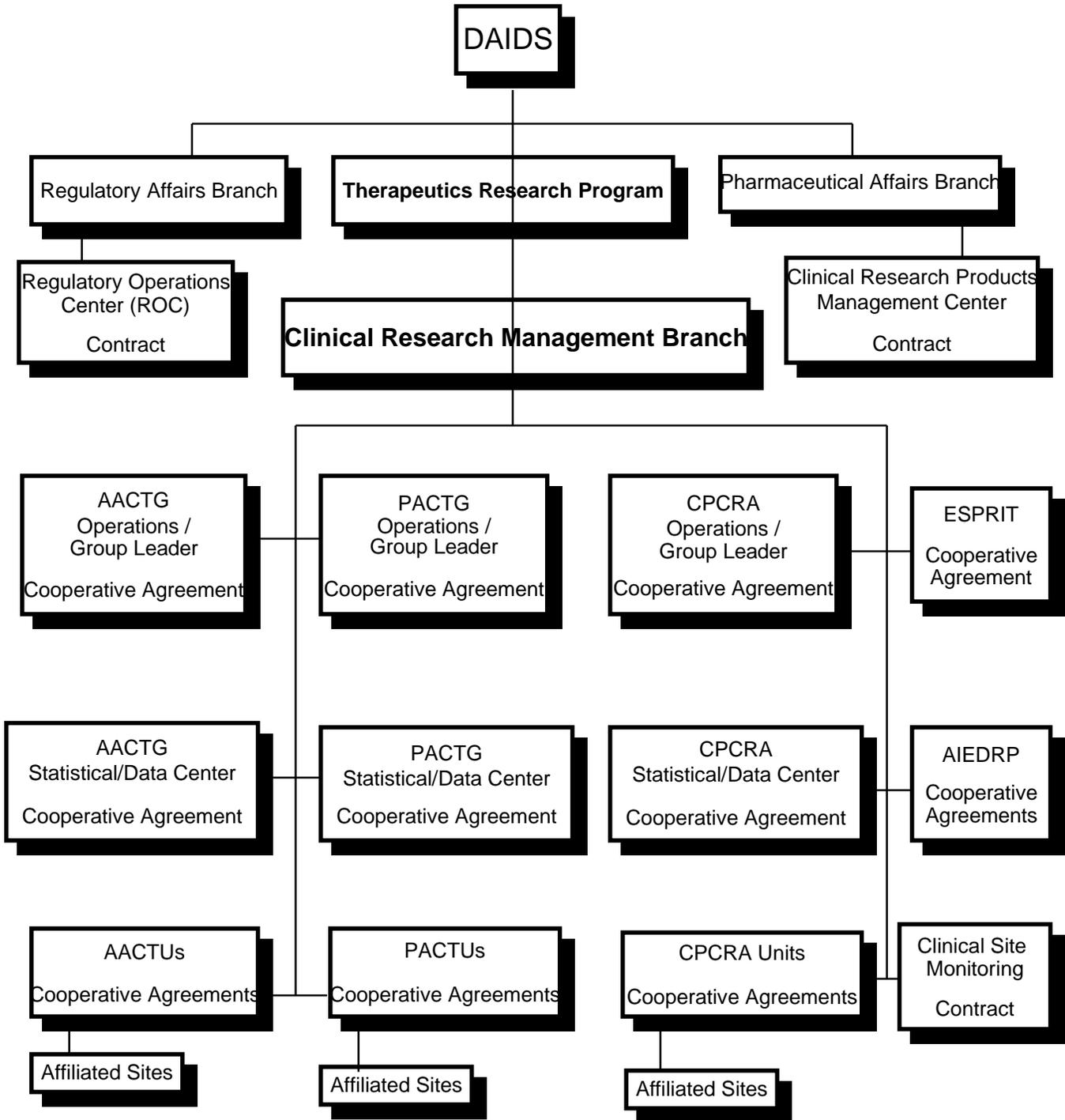
The Therapeutics Research Program (TRP) is responsible for the following major programs:

- **Acute Infection and Early Disease Research Program (AIEDRP)**
- **Adult AIDS Clinical Trials Group (AACTG)**
- **Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT)**
- **National Cooperative Drug Discovery Groups--OI (NCDDG)**
- **Pediatric AIDS Clinical Trials Group (PACTG)**
- **Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)**

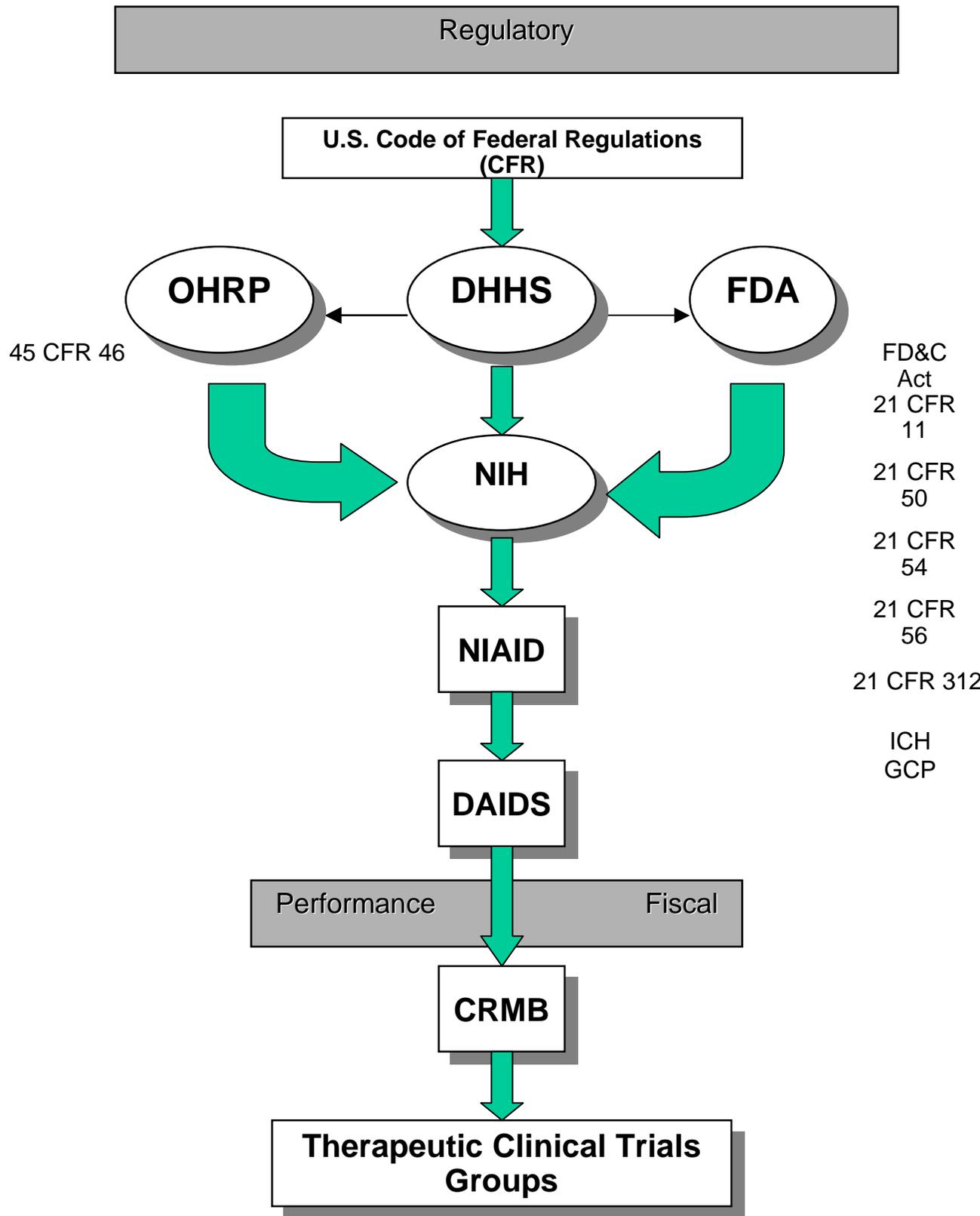
# Financial Support



# TRP Financial Support



# Oversight



# RAB & PAB Responsibilities

DAIDS

## Regulatory Affairs Branch

*Chief, MaryAnne Luzar, Ph.D.*

### Responsibilities:

- FDA Liaison
- File Investigational New Drug Applications (INDs) with the FDA
- Clinical Trials Agreements (CTAs) and Letters of Understanding (LOUs)
- Manage Regulatory Operations Center Contract
- Informed Consent Policy
- Serious Adverse Experience (SAE) Reporting
- Site Registration
- Site Training on Regulatory Issues
- OHRP Liaison/Prisoner Participation

## Therapeutics Research Program

*Assoc. Director, Bill Duncan, Ph.D.*

## Pharmaceutical Affairs Branch

*Chief, Ana Martinez, R.Ph.*

### Responsibilities:

- Assure that Investigational Drugs are Handled in Accordance with Federal/international Regulations
- Participate in Protocol Development and analysis as protocol team members
- Liaison with Pharmaceutical Companies
- Manage Clinical Research Products Management Center (CRPMC) Contract
- Review & Approve Site Pharmacies
- Oversee Monitoring of Site Pharmacies

# TRP Responsibilities

DAIDS

**Therapeutics Research Program**

*Assoc. Director, Bill Duncan, Ph.D.*

**Regulatory Affairs Branch**

*Chief, MaryAnne Luzar, Ph.D.*

**Pharmaceutical Affairs Branch**

*Chief, Ana Martinez, R.Ph.*

**Pediatric Medicine Branch**

**OI Research Branch**

**HIV Research Branch**

**Clinical Research  
Management Branch**

## Responsibilities of Medical Officers include:

- Develop NIAID extramural research agenda.
- Maintain expertise in the field of HIV therapeutic research.
- Provide leadership, facilitate growth and advancement of research.
- Participate in protocol development and analysis as a protocol team member.
- Ensure correct management of protocols.
- Present research concepts and protocols to the DAIDS Clinical Science Review Committee (CSRC).
- Provide medical safety monitoring for individual protocols and across all protocols.
- Liaison to other NIH Institutes and Offices; the FDA and other government agencies; and the public regarding HIV therapeutic research.
- Ensure that protocols are updated as new information regarding safety and drugs becomes available.

# TRP Responsibilities

DAIDS

**Therapeutics Research Program**  
*Assoc. Director, Bill Duncan, Ph.D.*

**Regulatory Affairs Branch**  
*Chief, MaryAnne Luzar, Ph.D.*

**Pharmaceutical Affairs Branch**  
*Chief, Ana Martinez, R.Ph.*

Pediatric Medicine Branch

OI Research Branch

HIV Research Branch

**Clinical Research  
Management Branch**

## Responsibilities include:

- Oversight and Management:
  - Annual performance review
  - Budgets
  - Human Subject Assurances
  - Policies and procedures
  - Site establishment
  - Site evaluation
  - Site closure
- Management of Clinical Site Monitoring Group (CSMG) contract
- Liaison with Community Constituency Group (CCG) committees
- Education, Training and problem resolution

**Clinical Research Management Branch  
(CRMB)**

*Chief, Fred Batzold*

**AACTG  
Coordinator**  
*Margaret Rodgers-McKenna*

**AIEDRP  
Coordinator**  
*Glenn Sturge*

**CPCRA  
Coordinator**  
*Judy Brooks*

**CSMG  
Project Officer**  
*Pam Scanlan*

**PACTG  
Coordinator**  
*Karen Reese*

**Statistical Centers  
Coordinator**  
*Peter Gilbert*

**Financial Management  
Specialist**  
*John Brooks*

**Program Analyst**  
*Annice Bergeris*

**Clinical Program  
Coordinator**  
*Mieko Maeshiro*

**Special Projects**  
*Karen Oseekey*

**Special Projects**  
*Margaret Matula*

## **D. BUDGET/GRANT PROCEDURES**

### **CARRYOVER PROCESS**

The use of un-obligated funds remaining in a grant account at the end of a budget period is at the discretion of NIAID. A programmatic evaluation will determine the best use of the funds, which may include consideration of a carryover request. Carryover is not automatic in a cooperative agreement (U01). If funds remain at the end of the grant year, the grantee may formally request a carryover of all or a portion of these funds. NIAID will consider the request based on a well-justified need. Each carryover request is considered separately.

NIAID will not consider a carryover request until the Financial Status Report (FSR) (OMB Form 269) is received from the grantee after verifying that funds remain in the grant account. The FSR is due 90 days after the end of the budget period.

The formal carryover request must:

1. Specify the amount to be carried over.
2. State the reason the funds remain un-obligated.
3. State how the funds will be spent; show direct costs, facilities and administrative costs, and provide a line item budget using the budget pages from a PHS 2590 form.
4. Explain the impact the use of the funds will have on the project.
5. Be signed by both the PI and an institutional official.
6. Be submitted to the Grants Management specialist and copied to the CRMB representative.

NIH recommends that grantees use e-mail to send administrative requests requiring approval, such as: change in PI, transfer of substantive programmatic work, reductions in effort, no-cost extensions, carryover of funds, and significant re-budgeting. For more information and advice, see the notice in the NIH Guide at:  
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-009.html>.

### **KEY PERSONNEL CHANGES**

Per the administrative terms included in the NGA:

If, for any reason, the Principal Investigator should change during the time of this contract, prior notification in writing must be given to the NIAID Program Coordinator for approval of a replacement. In addition, NIAID must be notified of any anticipated changes of a Subunit Principal Investigator, Clinical Coordinator (if applicable), Pharmacist, Study Coordinator, or other key personnel.

### **NONCOMPETING CONTINUATION APPLICATION**

The Type 5 application is due 60 days before the end of the current budget period. Approximately 2 months before the due date, CRMB will send out a letter detailing the requirements for this application and the Total Cost Dollars available.

## **NOTICE OF GRANT AWARD (NGA)**

The NGA includes:

1. A cover letter with general information
2. Section I - Detailed award data including a categorical breakdown and recommended future year total cost support
3. Section II - Payment/hotline information
4. Section III - Administrative terms and conditions of award

The administrative terms and conditions of award include details specific to this award including any restrictions, reasons for corrections, offsets, or carryover information. If there is a restriction, it may also include instructions on what is needed to remove the restriction.

## **RE-BUDGETING**

Re-budgeting of funds within a grant year may be done at the discretion of the Principal Investigator without prior approval by NIAID with two exceptions.

1. No funds may be moved in or out of the subject care category.
2. Significant re-budgeting, whether or not the particular expenditure(s) requires prior approval under rules governing budget changes. Significant re-budgeting occurs when expenditures in a single direct cost budget category deviate (increase or decrease) from the categorical commitment level established at the time of the competing award by more than 25 percent of the total costs awarded.

## **E. SITE/CENTER ESTABLISHMENT**

### **E.1. Site/Center Establishment Process**

The principal investigator (PI) at each clinical site/center participating in Division of AIDS (DAIDS)/Therapeutics Research Program (TRP) sponsored research is the primary individual responsible for establishing a clinical research site/center and ensuring that the site is staffed with qualified individuals experienced in the conduct of clinical trials research. The responsibilities also include establishment of internal policies and procedures that are in keeping with the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP) Guidelines to protect research subjects and produce reliable study information.

### **E.2. Site/Center and Pharmacy Establishment Requirements**

Site and pharmacy establishment information is to be submitted to the Clinical Research Management Branch (CRMB) Program Coordinator when a new site/pharmacy is initially opened. Site and pharmacy plans are also to be submitted for any additional affiliated sites.

Two important activities must take place before a new site/center may register for any study protocol: 1) Site Establishment and 2) Pharmacy Establishment.

Site/Center-Pharmacy establishment is required for all clinical sites/centers conducting research studies for which the DAIDS holds the Investigational New Drug Application. For other studies, site/center pharmacy establishment may be required as deemed necessary by DAIDS.

The site establishment form and pharmacy plan provide DAIDS/TRP with important personnel and clinical site information that assists with communication between the clinical sites/centers and DAIDS during the project period. All sites/centers must be established before protocol registration can take place.

The site establishment form is to be submitted to the appropriate CRMB Program Coordinator when a new site is opened or when key personnel changes occur during the project period. The pharmacy plan is to be submitted to the Chief of the Pharmaceutical Affairs Branch

Key Personnel are the PI, study coordinator, and pharmacist of record at the clinical research site/center and any affiliated sites/centers. Usually, those individuals named on the site establishment and pharmacy plans are considered to be key personnel.

For purposes of site/center establishment, key personnel are considered to be the PI, study coordinator and pharmacist at the clinical site/center and any affiliated sites/centers.

### **E.3. Affiliated Sites/Centers**

Affiliated sites/centers may only be established if:

1. The Clinical Research Management Branch and the Clinical Trials Group of which the sponsoring site/center is affiliated have given approval.
2. The sponsoring clinical site/center has demonstrated the capability to effectively conduct clinical trials and has met all performance standards that have been set by the respective clinical trials group.
3. The site/center has the appropriate staff that has time to provide oversight and guidance to the affiliated site/center staff.
4. At least ten subjects will be actively followed on-study each year at the affiliated site/center.
5. A separate site/center Establishment Form and Pharmacy Plan are required for each site/center and each affiliated site/center.

**NOTE:** New sites/centers will not be approved during the final year of a project period.

## **F. CLINICAL RESEARCH SITE/CENTER MANAGEMENT**

### **F.1. Policy**

All national and international clinical research sites/centers participating in studies sponsored by DAIDS are required to develop and maintain a management plan that describes the ongoing management and assessment of the clinical research activities.

### **F.2. Responsibility**

As stated on the Food and Drug Administration (FDA) Form 1572, the Principal Investigator (PI) assures that the investigator will personally conduct or supervise the clinical trial, and maintain accurate and complete research records.

To ensure compliance with other Federal and associated regulations and guidelines, the DAIDS requires that:

- A. The PI accepts ultimate responsibility for the quality of the data, subject safety, protocol adherence for all NIAID sponsored studies conducted at their sites/centers and the overall function of the clinical research site/center.
- B. The PI agrees to: 1) conduct the study/studies in accordance with the current protocol and standards of Good Clinical Practice (GCP), 2) be responsible for obtaining an Institutional Review Board (IRB)/Ethics Committee (EC) approval for the clinical trial and the informed consent process, 3) assure that the informed consent process is conducted according to the Office for Human Research Protections (OHRP) regulations and FDA guidelines and 4) comply with the National Institutes of Health (NIH) "Requirement for Education on the Protection of Human Subjects" for research investigators and key personnel involved in the research project.
- C. The PI agrees to personally provide direct oversight for those responsibilities that are delegated to other staff and further assures that all individuals involved in a study have been informed about their obligations. In the absence of the PI, a sub-investigator is to be designated as responsible for the day-to-day management of the clinical research site/center. Some institutions may require personnel changes to be approved by the IRB or EC.

D. The PI accepts responsibility for study activities at any sites/centers affiliated with a main site/center. This includes assuring the quality of the data collected, subject safety and adherence to current protocols. The PI should assure that the affiliated sites/centers are conducting Quality Assurance/Control activities and that the affiliated pharmacy is visited to review the research activities.

**Note:** It is recommended that the PI visit all affiliated sites/centers at least annually and meet with the affiliated sub-investigators at least three times a year.

### **F.3. Elements of Clinical Research Site/Center Management**

The DAIDS/TRP requires that each PI address these general elements in defining how the clinical research will be conducted.

Clinical Research Site/Center Administration  
Staff Education and Training/Certification  
Communication  
Protocol Compliance Activities (Quality Assurance/Quality Control)  
Regulatory Compliance  
Pharmacy Compliance  
Management of Laboratory Specimens  
Community Advisory Board  
Management Operations Evaluation

#### **Evaluation**

Staff at each site/center should develop a system for the annual review of overall clinical research site/center management functions. This evaluation should provide the opportunity to evaluate processes and procedures and allow for efficiencies to be incorporated into site/center operations.

#### **Review**

Staff from the DAIDS/TRP or designees may periodically review site/center management activities and/or visit the site/center to discuss management operations.

A copy of this plan is to be kept on file at the site/center.

#### **F.4. Clinical Research Site/Center Management Guidelines**

To better and more consistently manage the clinical research conducted at multiple sites, the Therapeutics Research Program (TRP) of the Division of AIDS (DAIDS) has developed guidance to assist staff at sites/centers in meeting management and regulatory obligations. The overall management of each site/center may vary but there are several functional areas that require close adherence to Federal regulations.

Staff at all sites/centers are required to develop a Clinical Research Management Plan that incorporates each of the **required elements** listed below. Each element must be developed in a plan for managing clinical research at a site/center. Sites/centers may vary on how they choose to implement this requirement. (The information included in the required elements is typically the type of documentation that the FDA would review during an on-site “for cause” audit).

- **Clinical Research Site/Center Administration**
- **Staff Education and Training**
- **Communication**
- **Quality Assurance (QA) and Quality Control (QC)**
- **Regulatory Compliance**
- **Pharmacy Compliance**
- **Management of Laboratory Specimens**
- **Community Advisory Board**
- **Management Operations Evaluation**

##### **F.4.A. Clinical Site/Center Administration** - Site/center files should include:

- A. Organizational structure of the clinical research site/center and affiliated sites/centers, including organizational charts and job titles
- B. Standard operating policies and procedures (SOPs). For example, a copy of the Table of Contents from the site/center SOP/Policy Manual could be included

- C. Job descriptions for all staff
- D. Documentation of annual review and assessment of staff workload/turnover
- E. Copies of licenses and up-to-date curriculum vitae (CVs) of professional staff (MD, PA, RN, RPh, etc.)
- F. Documentation of annual review/meeting with business/budget/fund accounting officials
- G. Subject screening logs

**F.4.B. Staff Education and Training** -Site/center files should include:

- A. Annual and continuing education/training, including annual updates, required by the site/center. A listing of required training at the site/center and the names of the individuals who attended the training is sufficient. For example, some sites/centers require annual updates on Good Clinical Practices.
- B. NIH/Group/Program education/training. Names of staff members and dates when training took place along with a description of the training are sufficient. Annual updates may include typical training topics such as:
  - 1. Orientation to the Clinical Trials Group/Program
  - 2. Clinical Trials Group and DAIDS Policies and Procedures
  - 3. Computer system(s)/ Electronic documentation
  - 4. FDA Guidance for Industry and International Conference on Harmonization: Good Clinical Practice: Consolidated Guidance
  - 5. Ongoing/new protocols
  - 6. Orientation and evaluation of new staff
  - 7. Proper handling and/or processing of
    - a. Biohazardous materials
    - b. Storage of specimens
    - c. Specimen shipping
    - d. Specimen tracking
  - 8. NIH "Requirement for Education on the Protection of Human Subjects" for research investigators and key personnel involved in the research project.

**F.4.C. Communication** - Some or all of this information may be covered in the site/center SOPs. If that is the case, simply provide a copy of that document, supplementing where necessary. If not, site/center files should include a description of the flow/dissemination of information at the site/center, any affiliated sites/centers, the operations center, and the statistical/data management center and include; for example:

- A. Staff meetings (PI/other investigators, nurses, study coordinators, pharmacists, laboratory personnel, data managers).
- B. Meetings between the sponsoring site/center designee with any affiliated site/center staff.
- C. Distribution of information memos, e-mails, and minutes of meetings.
- D. QA/QC findings/reports.
- E. Distribution of protocol-related information such as clarification memos, start-up call minutes and amendments.
- F. Distribution of information from DAIDS and Clinical Trials Group/Program. For example, revised SOPs, announcements and memos.
- G. Distribution of evaluation and routine performance reports from the Clinical Trials Group/Program.
- H. Distribution of monitoring site visit reports.
- I. Description of tools/aids developed by the site/center to document communication.

**F.4.D. Quality Assurance (QA) and Quality Control (QC)** - Some or all of this information may be covered in the site/center Quality Management Plan. If that is the case, simply provide a copy of that document.

Documentation of internal research record audits needs to be maintained on site and include:

- A. Name of clinician responsible for QA and individual responsible for QC.
- B. Description of the process for conducting QA and QC reviews at a site/center. For example: When are source documentation and protocol specific procedures for the initial subjects reviewed when a new protocol is started?
- C. Copies of tools/aids that are used for implementing QC measures. Some of those listed below may not be applicable to every site/center.
  - 1. Weekly/monthly reports
  - 2. QC reports
  - 3. Visit reminders
  - 4. Data entry and transmission report
  - 5. Error correction reports

6. Delinquency lists
7. Data retrieval programs
8. Data queries
9. Other tools/aids developed by site/center

D. QA audits - The following information shall be reviewed in the source document for every research record that is selected for initial QA review.

1. Informed consent and subject education
2. Eligibility criteria
3. Scheduled laboratory tests and procedures
4. Concomitant medications
5. Prohibited Medications
6. Drug dosing
7. AE identification and reporting
8. Clinical endpoint identification
9. Missed visit and follow-up of identified trends from the initial review

**NOTE: A minimum of 10% of the research records for each protocol shall be reviewed overall. Individual groups/protocol teams may require greater levels of QA/QC.**

E. Copies of tools/aids that are used for QA. Some of the following examples may not be used at every site/center.

1. Worksheets
2. Monthly data reports
3. Site/center evaluation reports
4. Logs
5. Summary forms
6. Monitoring site visit reports
7. Other tools/aids developed by site/center

F. Reporting QA results and documentation of QA audit findings should include:

1. Name of reviewer
2. Date of review
3. Records that were reviewed including the name of the CRFs
4. Specific contents that were reviewed in the record
5. Time period covered by the review
6. Results of review
7. Assessment of review
8. Describe how QA results are communicated to staff

G. Evaluation of the results of both QA and QC:

1. Identification of problem areas
2. Communication to site/center staff
3. Development of corrective action
4. Implementation of corrective actions
5. Evaluation of corrective actions

#### **F.4.E. Regulatory Compliance**

A. Site/center personnel will need access to:

1. US Federal Regulations: 45CFR46, 21CFR11, 50, 56 and 312
2. FDA Guidance for Industry: E6 and Good Clinical Practice: Consolidated Guidance

B. Sites/centers files need to include documentation that:

1. All study files and CRFs are: securely stored with limited access, and are available in the event of an audit by the study sponsors, local regulatory agencies and other regulatory agencies such as the FDA or designees.
2. Site/center staff are identified for maintaining regulatory files and ensuring that files are up-to-date and properly filed.
3. All required regulatory documents as listed in the DAIDS Source Documentation procedures are accessible to staff.

4. The internal process is documented for submission to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or the DAIDS' Regulatory Operations Center (ROC).
5. Copies are available for tools/aids used by the site/center to track and maintain records of both IRB/EC and ROC submissions and approvals.

C. Letters or Notices of the Food and Drug Administration:

NOTICE TO NIH GRANTEEES/CONTRACTORS REGARDING LETTERS  
OR NOTICES FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Release Date: September 22, 2000

Notice: OD-00-053

National Institutes of Health

Many NIH grantees/contractors conduct clinical research that involves a drug, biologic or device for which there is a Food and Drug Administration (FDA) Investigational New Drug Application (IND) and/or Investigational Device Exemption (IDE). When the NIH funds all, or part, of a clinical study that is being conducted under an IND and/or IDE, it is important that the NIH be knowledgeable about any significant communications with the FDA about that study.

In order to keep the NIH informed and comply with 45 CFR 74.51 (f), the awardee institution must report FDA communications to the awarding Institute(s) or Center(s) within 72 hours of receiving (through the principal investigator or any other persons acting on behalf of the awardee) a copy of the communication or upon being informed (through the principal investigator or any other person acting on behalf of the awardee) of the FDA communication, whichever occurs first. Failure to comply with this requirement may result in corrective and /or enforcement action.

By statute, the FDA communicates with the sponsor of the IND or IDE. The sponsor may, or may not, be the NIH awardee institution or NIH-funded principal investigator. FDA regulation, 21 CFR 312.55, outlines the responsibilities of sponsors to keep each participating investigator informed during the course of the study. Thus this notice to the awarding Institute (s) and Center(s) serves to complete the information loop. Awardee institutions must immediately notify the awarding Institute(s) and/or Center(s) of any of the following communications from the FDA regarding the research.

1. Warning letters: letters that are sent to you and/or to the commercial sponsor(s)

2. Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE letters)
3. Notice of Opportunity for Hearing (NOOH)
4. Notice of Disqualification
5. Consent Agreements
6. Clinical hold letters that pertain to breaches of either Good Manufacturing Practices, Good Clinical Practices or other major issues requiring significant changes in the protocol. The notification should be made in writing, but may be done by phone, if a written notice would delay the notification. The notification shall include a statement of the action taken or contemplated and the assistance needed to resolve the situation. The awarding Institute(s) and Center(s), NIH and HHS shall, pursuant to 45 CFR 74.53, have access to the FDA communications received by the grantee/contractor and other records of the grantee/contractor that are pertinent to the grant/contract.

Web site: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html>

D. Interruption of research activities due to an Office of Human Research Protections (OHRP) or Food and Drug Administration (FDA) action

1. The Principal Investigator (PI) is to notify the CRMB Program Coordinator by phone or email that an OHRP or FDA action has been initiated. A copy of the OHRP or FDA correspondence that describes the action/s that have been taken is to be faxed/emailed to the Program Coordinator.
2. The Program Coordinator is to be kept apprised of any further OHRP or FDA actions during the interruption of research activities. Copies of any correspondence that describe changes from the initial action are also to be faxed/emailed to the Program Coordinator.

E. Resumption of research activities after an OHRP or FDA action

1. The PI is to notify the CRMB Program Coordinator when the OHRP or FDA permits resumption of research activities and to advise the Program Coordinator about any special conditions required by OHRP or the FDA. A copy of the OHRP or FDA correspondence that permits research activities to continue is to be faxed/emailed to the Program Coordinator

**F.4.F. Pharmacy Compliance** - Site/center files shall describe how investigational products are handled. The DAIDS approved pharmacy plan that is on file at the site/center/pharmacy is sufficient to meet this requirement.

**F.4.G. Management of Laboratory Specimens** - Site/center files shall describe the management system for the collection, processing, storage and transportation of laboratory specimens. Reference to a site/center laboratory processing manual is sufficient for this section. If a laboratory manual is not available, this could be done with internal SOPs that describe:

A. Coordination between clinical sites/centers and laboratories and include:

1. Scheduling visits to ensure that specimens are obtained and processed based on protocol requirements
2. Proper completion of laboratory forms
3. Proper processing of specimens and shipment to outside laboratories
4. Reporting of test results
5. Correction of errors detected/reported by data/statistical centers
6. Storage conditions that provide for proper temperature, boxes, and vials

B. Periodic inventory of specimens

C. Quality of specimen management that includes:

1. Verification that the label is intact and label information is correct and legible
2. Tracking of specimens, forms, and related paperwork
3. Maintenance records and monitoring systems for freezer(s), refrigerator(s), incubator(s) and other equipment
4. Maintenance, calibration and repair records for instrumentation

D. Data capture and transfer mechanisms (e.g. software, hardcopy, logging-in, tracking, shipping, storage and error correction and updating).

**F.4.H. Community Advisory Board (CAB)** - A file on site shall describe the sites/centers' mechanism for incorporating CAB recommendations into the recruitment of subjects at the site/center. Most of this information is already available as part of the site/center Grant application. Include the following information:

A. Compliance with Group/Program requirements. For example, if the Group/Program has requirements for meeting attendance, are funds available for reasonable expenses, including representation at annual Group/Program meeting(s)?

B. Are CAB members representative of the HIV-infected catchment area?

C. Are CAB meetings regularly scheduled?

D. How does the staff communicate with the CAB?

E. What is the principal investigator's involvement?

**F.4.I. Outreach** - A file on site shall describe outreach endeavors. The inclusion of women and minorities in all aspects of site/center activities including subject recruitment and site/center staffing should be emphasized. Most of this information is already available as part of the site/center Grant application. If not, describe:

A. Subject recruitment

1. Community meetings/lectures
2. Local newspapers/radio advertisements
3. Chart review
4. Use of websites

B. Inclusion of women and minorities in activities of recruitment and site/center staffing

**F.4.J. Management Operations Evaluation** - A file on-site needs to describe the process of review, evaluation and revision of management operations. For example:

A. Evaluation of findings from internal QA and QC activity

B. Identification of performance areas that need improvement

C. Implementation of corrective actions

D. Periodic review of management operations to ensure staff adherence

E. Annual review of management operations for evaluation of effectiveness and needed changes

## **F.5. Prisoner Participation in DAIDS-Sponsored Therapeutic Clinical Trials**

The SOP, “Prisoner Participation in DAIDS-Sponsored Therapeutic Clinical Trials” is divided into two sections:

**Instructions** for obtaining approval for prisoner participation

- Part 1. Obtain IRB approval for participation of prisoners.
- Part 2. Actions if a study subject becomes incarcerated after enrollment in a protocol.
- Part 3. Actions while research activities are suspended.
- Part 4. Actions for protocols that were NOT reviewed by an OHRP-approved IRB for prisoner participation.
- Part 5. Registration for prisoner participation.

**Definitions** to provide further clarification of the terms and procedures.

- A. DAIDS/TRP approval for potential prisoner participation.
- B. IRB approval of research for prisoner participation.
- C. Agreement between institutions.

If you have any questions about implementation of the SOP, please contact your CRMB Program Coordinator at (301) 496-8214.

### **F.5.A. Instructions**

#### **Part 1. Obtain Institutional Review Board/Ethics Committee (IRB) approval for participation of prisoners.**

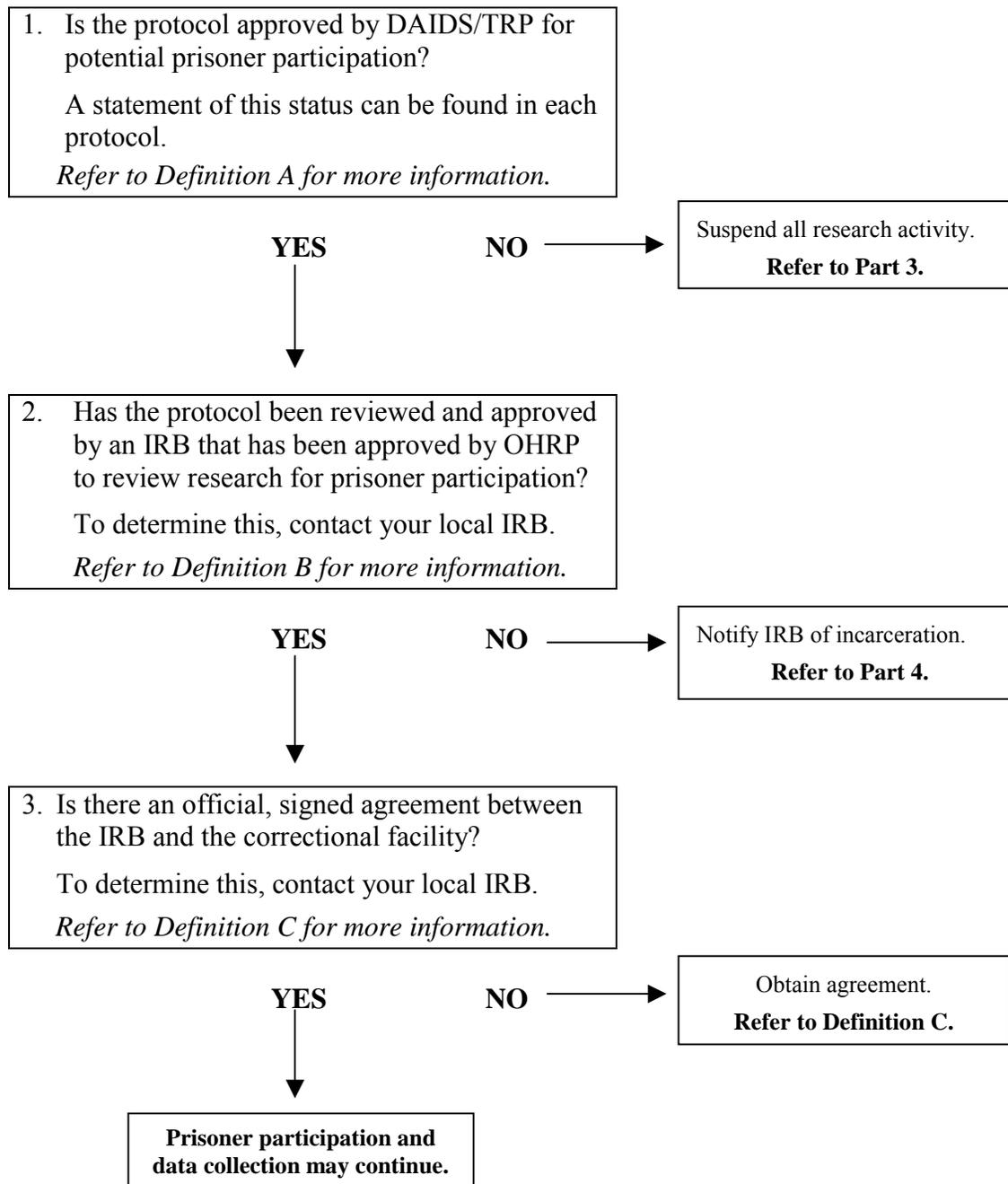
- Determine if the DAIDS-sponsored therapeutic protocol has been approved by DAIDS/TRP for potential prisoner participation. **Refer to Definition A. (DAIDS/TRP approval for potential prisoner participation) on page F-14.**
- Submit each protocol that has been approved by DAIDS/TRP for potential prisoner participation to the local IRB for their review and approval of prisoner participation. **Refer to Definition B. (IRB approval of research for prisoner participation) on page F-15.**
  - 1. The principal investigator (PI) must notify the IRB of the intent to potentially enroll or follow prisoners as study subjects.
- DAIDS/TRP recommends that all sites request IRB review and approval for prisoner participation at the IRB’s initial review of all DAIDS-sponsored therapeutic protocols that have been approved for potential prisoner participation.
  - 2. The IRB should have an agreement with the prison indicating that the prison will comply with the appropriate human subjects regulations. **Refer to Definition C (Agreement between Institutions) on page F-16.**

3. If the IRB reviews the protocol and determines that it is **NOT** appropriate for prisoner participation, incarcerated subjects may **not** be enrolled or followed on the protocol by the site.
- Upon IRB approval, submit the appropriate documentation to the Regulatory Operations Center (ROC) to register for prisoner participation. **Refer to Part 5 (Registration for prisoner participation) on page F-13.**

**Instructions (continued)**

**Part 2. Actions if a study subject becomes incarcerated after enrollment in a protocol.**

Follow the flow diagram below to determine what actions, if any, the site will need to take if a study subject becomes incarcerated after he or she has been enrolled in a DAIDS-sponsored therapeutic clinical trial.



## **Instructions (continued)**

### **Part 3. Actions while research activities are suspended.**

- The subject does not have to be permanently withdrawn from the protocol; however, data collection and efforts to contact the subject for research-related information are to be suspended.
- Investigational drugs or any study products provided by DAIDS may not be supplied to incarcerated individuals while the research is suspended.
- Incarcerated individuals who are receiving FDA-approved medications by prescription may continue to receive these medications according to policies of the prison.
- Once the subject is released from the prison, participation in the study may resume with the subject's continued consent.

### **Part 4. Actions for protocols that were NOT reviewed by an OHRP-approved IRB for prisoner participation, but have been reviewed and approved by DAIDS/TRP for potential prisoner participation.**

- Within 5 (five) working days of becoming aware of the subject's incarceration, the PI must notify the IRB Chair in writing, that a subject has become incarcerated while on-study.
- The subject may continue on-study if the IRB Chair determines that it is in the best interest of the subject to continue in the protocol pending full IRB review. If not, research activities must be suspended—refer to Part 3 for instructions.
- The protocol must be reviewed for prisoner participation, as outlined in Definition B, at the next possible full IRB review. Refer to Definition B for information on the requirements.
- If the IRB reviews the protocol and determines that it is NOT appropriate for prisoner participation, research activities must be suspended. Refer to Part 3 for instructions.
- Upon IRB approval, the site must submit the appropriate documentation to ROC to register for prisoner participation. Refer to Part 5 for instructions.

### **Part 5. Registration for prisoner participation.**

Submit the following to ROC for review:

1. Completed Site Registration Checklist
2. Documentation of IRB approval for prisoner participation in the form of an IRB Approval Letter that includes:
  - a. The signature of IRB designee (usually the Chair or Administrator)

## **Instructions (continued)**

b. Confirmation of the following:

- (i) The prisoner representative was present during the review.
- (ii) OHRP has a copy of the IRB roster on file.
- (iii) The IRB determined that the required elements in Section 46.305 were met and that one of the categories in Section 46.306 permits the research to go forward.

3. A copy of the IRB-approved prisoner informed consent form

- ROC reviews and approves the completed site registration documentation required for prisoner enrollment.
- ROC registers approved sites to enroll and follow prisoners as subjects in the specified protocol.
- ROC informs OHRP of sites that are registered for prisoner participation for each DAIDS-sponsored therapeutic protocol.

### **F.5.B. Definitions**

#### **A. DAIDS/TRP approval for potential prisoner participation.**

The Clinical Science Review Committee (CSRC) of DAIDS/TRP reviews all DAIDS-sponsored therapeutic protocols for consideration of appropriateness for prisoner participation:

1. Protocols considered for prisoner participation do not include placebos—the minimum treatment is always standard of care (as indicated by current Public Health Service guidelines).
2. Only protocols with treatment arms are considered. Observational and epidemiological studies are not approved by CSRC for potential prisoner participation.

As part of the CSRC review, RAB reviews each protocol to determine if the research is permissible for prisoner participation in accordance with:

1. 45 CFR 46.306 (a) (2) (D): “Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.” (The citation is 45CFR46.306(a)(2)(iv) in the 10-1-99 version from the Code of Federal Regulations.)

## Definitions (continued)

2. The local IRB must actively document its concurrence or non-concurrence with this determination.
3. Review for compliance with 45 CFR 46.305 is **NOT** done by DAIDS/TRP—that is the responsibility of the IRB.

The final determination of approval or disapproval of a protocol for prisoner participation is made by the Associate Director, TRP and Chief, RAB. A memo documenting the review of the protocol for potential prisoner participation and the final determination of whether or not prisoners may be included is completed, signed by both parties, and forwarded to OHRP.

- A statement is included in each DAIDS-sponsored therapeutic protocol indicating whether or not DAIDS/TRP has approved it for potential prisoner participation based on 45 CFR 46.306.

### **B. IRB approval of research for prisoner participation.**

The IRB must have approval from OHRP to review and approve research that involves prisoners.

1. If the local IRB does not have such an OHRP approval, the IRB may request it by contacting the appropriate OHRP Assurance Coordinator and submitting a revised IRB roster with a designated prisoner representative.
  - a. A list of Assurance Coordinators and their assigned regions is available at OHRP's Web site: <http://ohrp.osophs.dhhs.gov/dpa-staff.htm>
  - b. A secondary contact is the Director for Regulatory Affairs at OHRP, who is responsible for reviewing all institutional certifications related to HHS-supported research that involves prisoners.
2. The local IRB may review a study for prisoner participation in accordance with 45 CFR 46.305 without a prisoner representative IF the multicenter protocol has already been reviewed and approved for prisoner participation by another OHRP-approved IRB in accordance with 45 CFR 46, Subpart C. Contact RAB for information on this option.

The approved IRB must review the protocol for appropriateness of prisoner participation in accordance with 45 CFR 46.305 and 46.306.

The approved IRB must re-review the protocol for compliance with 45 CFR 46.305 and 46.306 if any of the following occur:

1. The protocol was not previously reviewed by the IRB for appropriateness of prisoner participation.
2. The IRB's prisoner representative was not present for the protocol review.

### **Definitions (continued)**

The following must be documented in the IRB minutes:

1. Presence of the prisoner representative during the protocol review.
2. Approval of the protocol for inclusion of prisoners is in accordance with 45 CFR 46.305 and 46.306.

The site is responsible for maintaining records of the IRB approval for inclusion of incarcerated subjects in their regulatory files.

### **C. Agreement between institutions.**

There should be an official, signed agreement between the IRB and the prison that states the following terms:

1. The IRB accepts responsibility for the research that is conducted in the prison.
2. The prison agrees to:
  - a. The conduct of research in their facility.
  - b. Comply with human subjects' protection regulations (45 CFR 46).
  - c. Accept the IRB's oversight of the research.

If either institution does not agree with the terms, research activities must be suspended. Refer to Part 3 for instructions.

Prisons do not need an OHRP Assurance or need to be covered by an Institution's Assurance if they are not actively involved in the research (i.e., prison staff do not consent subjects, participate in enrollment, or conduct study visits).

## **F.6. Transportation of Infectious Substances**

### **F.6.A. Air Transportation**

The International Air Transport Association (IATA) has implemented regulations governing the shipping of "Dangerous Goods" via air transport. The Department of Transportation (DOT), Centers for Disease Control (CDC), and other federal agencies have regulations regarding the shipment of infectious substances. However, since the IATA regulations are more comprehensive and stringent, it is recommended that the IATA regulations be used for all domestic and international air shipments. "Dangerous Goods (Class 6)" are defined as "articles or substances that are capable of posing a significant risk to health, safety, or to property when transported by air." This classification is further divided. One of the sub-divisions is "Infectious Substances (Class 6.2)." Any specimens from subjects known to be or expected to be HIV-infected are considered to be "Infectious Substances." Thus, such specimens must be identified, marked, labeled, documented, packaged, packed, and shipped in a manner specified in the IATA regulations.

### **F.6.B. Surface Transport Transportation (Interstate)**

- In addition to air transport, federal agencies also regulate surface transport.
- Department of Transportation (DOT) – Hazardous Materials Regulations cover highway, rail, and water transportation (49 CFR parts 100-185), and set standards for shipping contractors and shippers.
- CDC - 42 CFR 72 (Interstate Shipment of Etiological Agents) is currently undergoing revision.

### **F.6.C. International Shipments (Import and Export)**

- CDC regulates incoming infectious substances. It requires that an importer of infectious substances from outside the United States obtain an import permit and that the importer bear responsibility for safe packing, labeling, and contact information for foreign shipping personnel. Refer to the CDC Web site for more information:  
<http://www.cdc.gov/od/ohs/biosfty/imprtper.htm>
- When shipping infectious substances to other countries, the Department of Commerce export administration regulations (15 CFR Parts 742, and 774) must be followed. Also check specific regulations in the country of destination.

### **F.6.D. Training Sources**

- Courier as well as packaging companies offer training courses.
- National Laboratory Training Network (NLTN) is sponsored by the Association of Public Health Laboratories and Centers for Disease Control (CDC). Refer to the CDC Website for more information: <http://www.phppo.cdc.gov/dls/nltn>
- Other IATA accredited training courses are identified at the IATA Web site:  
<http://www.iata.org/cargo/dg>

### **F.6.E. Relevant Regulations/Guidelines**

- CDC - 42 CFR Part 72
- Biosafety in Microbiological and Biomedical Laboratories (BMBL) 4<sup>th</sup> Edition
- DOT - 49 CFR Parts 100-185 (Hazardous Materials Regulations)
- OSHA - 29 CFR 1910.1030
- United States Postal Service, Domestic Mail Manual CO23
- IATA Dangerous Goods Regulations

### **F.6.F. Relevant Web Sites**

- [www.cdc.gov/od/ohs](http://www.cdc.gov/od/ohs)
- [www.cdc.gov/od/ohs/biosfty/imprtper.html](http://www.cdc.gov/od/ohs/biosfty/imprtper.html)
- [www.cdc.gov/od/ohs/irsat/42cfr72.html](http://www.cdc.gov/od/ohs/irsat/42cfr72.html)
- [www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm](http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm)
- [www.osha.gov](http://www.osha.gov)
- [www.iata.org/cargo/dg](http://www.iata.org/cargo/dg)
- [www.text-trieve.com/dotrspa](http://www.text-trieve.com/dotrspa)

## **F.7. Site/Center Closure:**

These guidelines describe activities that will take place when clinical sites/centers close. These activities include: 1) subject follow-up and 2) proper disposition of drugs, study records, and specimens according to regulations and procedures of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

Site closure may be initiated by the Division of AIDS (DAIDS): 1) at the end of a funding period, 2) if there is a decline in subject enrollment, 3) if satisfactory standards of performance are not achieved, 4) if there is a failure to comply with regulatory requirements, and 5) if there is a failure to comply with terms of a financial agreement, if applicable.

Site closure of an affiliated site may also be initiated by the Principal Investigator (PI) of a sponsoring clinical site/center.

### **F.7.A. Site Procedures:**

1. A letter/e-mail from the PI is to be submitted to the Program Coordinator of the Clinical Research Management Branch (CRMB). If an affiliated site/center is going to close and subcontracts or other financial arrangements are in place, the letter will need to be signed by the business officials of both sites/centers.

The following information needs to be included in the letter:

- a. Reason for closure
  - b. Proposed date of closure
  - c. Status of all subjects for each protocol (on/off drug, on/off protocol, etc.)
  - d. A statement about any financial arrangements, budget period commitment dates, funding mechanism (subcontract or reallocation of existing award funds), and rebudgeting need to be included, if applicable.
  - e. Plan for disposition of study products, CRFs, pharmacy records and specimens
2. Any subjects still on-study may be transferred to another clinical trials site. Subjects not wishing to transfer will be discontinued from study/studies according to procedures mandated by the protocol. The Data Management Center (DMC) will turn off the randomization screens.
  3. Serious adverse experiences must continue to be reported to the DAIDS Adverse Experience Report (AER) Office for sixty days after discontinuation of study drugs for those subjects who are discontinued from studies. All subject deaths are to be reported according to the DAIDS Serious Adverse Experience Manual.
  4. The site/center will follow procedures for deregistration from all protocols according to the Site Registration Manual.

5. If study products are being dispensed as part of DAIDS protocols, the pharmacy will be audited after the last subject visit. All study products will be returned to the NIAID Clinical Research Products Management Center or other source. The DAIDS Pharmaceutical Affairs Branch (PAB) will oversee the return of study products.
6. Disposition of study specimens stored at the site/center will be completed before the site is closed per the Clinical Trials Group or protocol team requirements.
7. The DMC will address all data queries before site closure and all outstanding data entry must be completed before a site is closed. The sponsoring clinical site/center is responsible for resolving data queries when possible after an affiliated site/center closes. However, if a data query can only be resolved by accessing the subject's medical records residing at the closed affiliated site/center and if the staff at the sponsoring site/center do not have access or consent to review these records, the staff need to inform the DMC that the query cannot be resolved and specify the reasons.
8. A final monitoring visit will be conducted to identify any outstanding data requirements and verify disposition of all study products and specimens. The clinical site monitor will schedule a monitoring visit including a pharmacy audit, if applicable.
9. Case report forms (CRFs), including appropriate shadow files, and pharmacy records will be transferred to the sponsoring clinical site/center for storage when an affiliated site/center closes. If a sponsoring site/center is being closed, the Standard Operating Procedure for Storage of Case Report Forms and Pharmacy Records is to be followed.
10. The Regulatory Operations Center (ROC) will oversee shipment of CRFs and study records.
11. The ROC will remove the site from the clinical trials system directory.

Questions about site closure procedures should be directed to the CRMB Program Coordinator at (301) 496-8214.

## **F.8. Standard Operating Procedure:**

### **F.8.A. Purpose**

The purpose of this standard operating procedure (SOP) is to provide guidance to research personnel when a system of records is established. Documentation of source data is necessary for the reconstruction, evaluation, and validation of clinical findings, observations, and other activities during a clinical trial. Source documentation serves to substantiate the integrity of trial data, confirm observations that are recorded, and confirm the existence of subjects. This SOP also serves to ensure data quality by creating audit trails and enabling verification that data are present, complete, and accurate. In multi-site clinical trials it is important for documentation of source data to be standardized across all sites to ensure consistency of the trial data.

### **F.8.B. Scope**

This SOP is based upon: 1) the Code of Federal Regulations (CFR), 2) guidances that apply to the involvement of human subjects in clinical research, and 3) standards for good clinical practice (GCP). It is applicable to all Division of AIDS (DAIDS) funded clinical trial sites conducting therapeutic, vaccine, or prevention studies on human subjects, both domestic and internationally.

### **F.8.C. Instructions**

- In addition to the requirements for source documentation that are listed in this document, suggestions and/or comments are also included regarding implementation and references to the pertinent Federal regulations and/or guidances.
- A trial site is the location where the research is conducted and the term site is generally used in this document in place of the terms: unit, main unit, subunit, affiliated site, or center.
- All data must be verifiable and all documentation needs an audit trail.
- Always refer to local, state, institution, institutional review board (IRB)/independent ethics committee (IEC) policies and procedures and follow them if they are more stringent than DAIDS SOPs.
- Apply ALCOA\* to achieve data quality.
  1. **Attributable:** is it obvious who wrote it?
  2. **Legible:** can it be read?
  3. **Contemporaneous:** is the information current and in the correct time frame?
  4. **Original:** is it a copy; has it been altered?

5. Accurate: are conflicting data recorded elsewhere?

\*Source: "The Facts About Source Documents" by Stan W. Woollen, Presented at the 1999 DIA Annual Meeting

## F.8.D. Source Documentation SOP

<b>Addenda</b>	
Requirement	<ul style="list-style-type: none"> <li>• If source documentation is incorrect, incomplete, or otherwise deficient, it may be corrected/completed by making an additional entry or addendum to the source documentation. The later entry must be signed/initialed and dated.</li> <li>• All addenda must be signed and dated in present time by the person making the entry.</li> <li>• Sites must NOT modify past-dated source documentation in research records in an attempt to resolve deficiencies. Altering past-dated records is potentially fraudulent.</li> <li>• If it is noted in the research record that data are missing and those data are then obtained/found at a later date, its incorporation in the research record must be noted in the research record. The notation must be signed/initialed and dated.</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Identification of incomplete/deficient source documentation may occur by site staff during internal QA or by a monitor during a site visit.</li> <li>• Addenda that are not appropriately signed and dated are prohibited because such entries are not verifiable.</li> <li>• It is recommended that when including addenda to source documentation, the deficiency and the circumstances (if known) surrounding the situation be documented in a note.</li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Documentation Standards</u></li> <li>• <u>Error Corrections</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 Good Clinical Practice (GCP), Sections 4.9 and 5.18.4</li> <li>• Thompson Publishing Group, <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> </ul>
<b>Assent</b>	
Requirement	<ul style="list-style-type: none"> <li>• Assent of children and permission of parents or legal guardians as determined by the IRB/IEC is required as per the provisions of 45CFR46.</li> <li>• State/local law where the research is taking place defines the age of a minor and requirements for emancipation.</li> <li>• Local IRB/IEC determine the age for obtaining assent.</li> <li>• The requirement for assent of children and/or permission of their parents or legal guardians may be waived by the IRB/IEC as long as the criteria for waiving consent in the regulations (45CFR46.408c) are met.</li> <li>• Keep on file all versions submitted and approved by site's IRB/IEC.</li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 45CFR46, Subpart D</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• FDA Guidance: FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, Q&amp;A Nos. 47 and 48; and Page 5.</li> <li>• FDA Interim Rule: Federal Register, Vol. 66, No. 79, 24 April 2001, pp. 20589-20600.</li> </ul>

## Case Report Forms used as Source Documentation

Requirement	<ul style="list-style-type: none"> <li>• Case report forms (CRFs) may be used as source documents if they represent data collected for the study and are where data were initially recorded.             <ol style="list-style-type: none"> <li>1. If data are obtained at a later date (i.e., after the study visit) and are recorded on the CRF as source documentation, it must be signed/initialed and dated.</li> <li>2. If data are transcribed from another source onto the CRF, the CRF is not considered to be the original source document and it cannot be used as source documentation. Examples of data that are routinely transcribed from other sources include: laboratory results, radiology reports, histories documented in referral letters, etc.</li> </ol> </li> <li>• CRFs used as source documents are not meant to replace <u>ALL</u> source documentation—there will still be a need for progress notes, lab results, X-rays, etc.</li> <li>• CRFs used as source documentation need to be maintained and made available for review in the same manner as other source documents.</li> <li>• Also refer to the section on questionnaires for the procedures specific to those types of CRFs.</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• If a site chooses to use a CRF as source documentation, it should be used consistently as source documentation during the trial for all subjects at the site.</li> <li>• CRFs are an adjunct to other source documents and may be filed with the source documents.</li> <li>• As a source document, it is good practice for the original CRF to be signed/ initialed and dated by the individual who recorded the data on the CRF.</li> <li>• In the event of an FDA audit, the site needs to clearly indicate at the start of the audit, which CRFs are being used as source documentation.</li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Addenda</u></li> <li>• <u>Copies</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Error Corrections</u></li> <li>• <u>Inadequate Source Documentation</u></li> <li>• <u>Initials</u></li> <li>• <u>Questionnaires</u></li> <li>• <u>Storage of Source Documents</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312.62</li> <li>• FDA Guidance: E6 GCP, Sections 1.11, 1.51, 1.52, 4.9, 5.23, 5.5, and 6.4.9</li> </ul>
<b>Chart Note</b>	
Requirement	<ul style="list-style-type: none"> <li>• Refers to all notes related to study visits that are entered in the research or medical record by site staff. (e.g., progress note, nursing note, clinic note, etc.)             <ol style="list-style-type: none"> <li>1. This does NOT apply to source documents that originate outside the site since the individuals making the notations may not be involved with the study.</li> <li>2. Follow the institution's record-keeping procedures if they are more stringent.</li> </ol> </li> <li>• All data entries must be signed/initialed and dated:             <ol style="list-style-type: none"> <li>1. Each time a new entry is made.</li> <li>2. By the person making the entry.</li> <li>3. Entries by different people must be signed/initialed and dated by the individual making the entry.                 <ul style="list-style-type: none"> <li>➤ Exceptions:                     <ul style="list-style-type: none"> <li>✓ Multiple entries to a source document made by the same person on the same day require only one signature/initials and date on the page IF there have been no interim entries made by other individuals. It is incumbent upon the individual signing the source document to ensure that there have been no entries other than his/her own.</li> <li>✓ A single date on a document with multiple entries is permitted if all entries were made on that same date.</li> </ul> </li> </ul> </li> </ol> </li> </ul>

Suggestions	<ul style="list-style-type: none"> <li>• All chart notes and other source documentation should be filed in order by date to support the chronology of subject events.</li> <li>• Entries that continue across more than one page should be signed/initialed and dated on each page. Refer to local institution policy.</li> <li>• Refer to the Research Record section for requirements pertaining to hospital records subsequently used as source documentation.</li> <li>• Includes any note used to support:             <ol style="list-style-type: none"> <li>1. Data entered onto CRFs</li> <li>2. Eligibility criteria</li> </ol> </li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Addenda</u></li> <li>• <u>Copies of Outside Records</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Entry Criteria</u></li> <li>• <u>Error Corrections</u></li> <li>• <u>Inadequate Source Documentation</u></li> <li>• <u>Initials</u></li> <li>• <u>Research Record</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR11</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> <li>• FDA Guidance: E6 GCP, Section, 4</li> </ul>
<b>Communications: verbal</b>	
Requirement	<ul style="list-style-type: none"> <li>• Verbal communications pertinent to research data collection must be documented in the research record in enough detail to support the data collected.</li> <li>• Document in one of the following:             <ol style="list-style-type: none"> <li>1. Chart note</li> <li>2. Contact report (i.e., any written documentation of conversation that is signed and dated)</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• A third party communication may be used to document vital status and other situations.</li> <li>• Includes actual or attempted contacts with:             <ol style="list-style-type: none"> <li>1. Subject</li> <li>2. Parent/legal guardian</li> <li>3. Family members/significant other</li> <li>4. Friends</li> <li>5. Healthcare providers</li> <li>6. Other healthcare facilities</li> </ol> </li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance:E6 GCP, Section 4.9.1</li> </ul>

**Communications: written**

Requirement	<ul style="list-style-type: none"><li>• Written communications pertinent to research data collection must be documented in the research record.</li><li>• Documents must have appropriate identifiers to verify that they correspond to the specified subject.</li><li>• Includes documents such as the following examples:<ol style="list-style-type: none"><li>1. Letter</li><li>2. Memo</li><li>3. E-mail</li><li>4. Reply correspondence</li><li>5. Admission/discharge summaries</li></ol></li></ul>
Suggestions	<ul style="list-style-type: none"><li>• If no other documentation exists regarding written communications sent to the subject via special carrier (e.g., Fed Ex, Airborne, certified mail, etc.), it is recommended to retain copies of tracking forms/receipts.</li><li>• Includes actual or attempted contacts with:<ol style="list-style-type: none"><li>1. Subject</li><li>2. Parent/legal guardian</li><li>3. Family members/significant other</li><li>4. Healthcare providers</li><li>5. Other healthcare facilities</li><li>6. Other contacts identified by the subject</li></ol></li></ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"><li>• <u>Confidentiality</u></li><li>• <u>Identifiers</u></li></ul>
Reference	<ul style="list-style-type: none"><li>• FDA Guidance: E6 GCP, Section 4.9.1</li></ul>

**Compliance: study drug / agent**

Requirement	<ul style="list-style-type: none"><li>• Compliance data is to be captured as specified by the protocol.</li><li>• Document in one of the following:<ol style="list-style-type: none"><li>1. Chart note</li><li>2. CRF used as source document</li><li>3. Pharmacy records</li></ol></li></ul>
Suggestions	<p>To meet GCP Guidelines for documentation of compliance data, it is important to remember that compliance data has two components, quantitative data and qualitative data.</p> <ul style="list-style-type: none"><li>• Quantitative data that should be captured includes:<ol style="list-style-type: none"><li>1. Quantity of study drug/agent dispensed</li><li>2. Quantity returned, if any*</li><li>3. Reported number of missed doses</li></ol><p>*If the study does not provide the drugs/agents through the site or site pharmacy, but rather the subject secures drugs/agents through prescriptions filled at their own pharmacy, the information on quantity returned is not applicable.</p></li><li>• Qualitative data that should be documented in a chart note include:<ol style="list-style-type: none"><li>1. The directions for taking all study drugs/agents have been reviewed with the participant.<ul style="list-style-type: none"><li>➢ When study drugs/agents are initially provided.</li><li>➢ At intervals determined by the protocol.</li></ul></li><li>2. Deviations from the instructions or problems in following the instructions.</li></ol></li></ul>

	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Prescriber</u></li> <li>• <u>Prescriptions</u></li> <li>• <u>Study Drug/Agent</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.5.3, 4.6.5, 4.6.6</li> </ul>
<b>Computer Records (Computerized Systems / Electronic Records)</b>	
Requirement	<ul style="list-style-type: none"> <li>• When data are entered directly into a computer system, the electronic data in the computer system is the original source document.</li> <li>• A paper record (printout/hard copy/"print screen") of the electronic data is considered to be a copy.</li> <li>• Requirements for documentation, record keeping and record retention apply to computer records as they do for paper systems.</li> <li>• Computer records may be signed with an electronic signature.</li> <li>• One type of an electronic signature is when a user signs-on to a computer system using two (2) distinct identification components, such as an identification code (user name) AND a password.             <ol style="list-style-type: none"> <li>1. Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.</li> <li>2. Signed electronic records must contain information associated with the signing that clearly indicates all of the following:                 <ul style="list-style-type: none"> <li>➤ Printed name of the signer.</li> <li>➤ Date and time when the signature was executed.</li> </ul> </li> </ol> </li> <li>• If original source documents are signed with electronic signatures then it is necessary to certify to the FDA that the electronic signatures in the computer system are intended to be the legally binding equivalent of traditional handwritten signatures.             <ol style="list-style-type: none"> <li>1. The institution may submit certification for the employees as a whole to the FDA rather than on an individual basis.</li> <li>2. A principal investigator may submit certification for the research staff to the FDA in place of the institution.</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• If a paper record of electronic data used as a source document, the copy should be certified ONLY if the original, electronic file is not maintained.</li> <li>• Computer records may include information such as:             <ol style="list-style-type: none"> <li>1. Subject data, reports and/or results.</li> <li>2. E-mail communications pertaining to a subject or protocol management (e.g., directives from protocol chairs, site investigators to research nurses, etc.).</li> <li>3. IRB/IEC correspondence pertaining to a subject or study.</li> </ol> </li> <li>• If an institution's computer system does not meet the requirements of 21CFR11:             <ol style="list-style-type: none"> <li>1. Systems should be moving toward compliance—upgrade their system if they plan to use electronic records.</li> <li>2. FDA currently accepts existing hospital systems.</li> </ol> </li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR11</li> <li>• FDA Guidance: Computerized Systems Used in Clinical Trials</li> </ul>

**Concomitant Medication: non-study**

Requirement

- Document subject/caregiver reported use of concomitant medication, non-study drugs, and prohibited medication according to protocol requirements.

Suggestions

In addition to prescription medication, this includes non-prescription drugs such as aspirin, cocaine, heroin, vitamins, etc.

**Confidentiality**

Requirement

Inform Subject

- Subjects must be informed of the extent to which confidentiality of records identifying them will be maintained:
  1. Extent permitted by law.
  2. Personal information is not released without subjects' written permission.
  3. Subjects are not personally identified in any publication about the study.
  4. Data is to be identified by code (e.g., PID) outside of the site.
  5. Research records may be reviewed by representatives<sup>1,2</sup> of:
    - Food & Drug Administration (FDA) for studies under an IND
    - Office for Human Research Protections (OHRP)
    - National Institutes of Health (NIH)
    - Study monitors
    - Pharmaceutical companies involved in the study
    - Responsible IRB/IEC

<sup>1</sup>A potential subject, in the informed consent process, must be made aware of the appropriate representatives (listed in item #5) that may review all of his/her medical records (research specific or otherwise) that are held by the institution conducting the research.

<sup>2</sup>While the research-specific record is the document being monitored for compliance with regulations and guidelines, access to the full medical record held by the institution that is conducting the research must be available to monitors at the time of review for purposes of identifying supporting documentation of research record data.

Storage

- All research records must be securely stored:
  1. Double-lock when not in use.
  2. Restricted access during work hours and/or when unattended.
  3. Also refer to local institutional policies & procedures.

Labeling

All source documents must be labeled with subject identifiers to enable verification that the documents correspond to particular subjects.

Information Leaving the Site

If research records leave the site, follow local institution policy to ensure that confidentiality is maintained.

Suggestions	<ul style="list-style-type: none"> <li>• Subjects' written permission in DAIDS studies is obtained via the signed informed consent and/or signed release.</li> <li>• Non-site staff usually do not require information that would connect a subject to his/her study records. For this reason, PID/SID numbers should not be routinely used in hospital charts or medical records used by non-research personnel and/or charts/records outside of the site.</li> <li>• Examples of storing records under double-lock include:             <ol style="list-style-type: none"> <li>1. Lock on the office and lock on the file cabinet.</li> <li>2. Locked office inside a clinic that is locked when not in use.</li> </ol> </li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Identifiers</u></li> <li>• <u>Informed Consent</u></li> <li>• <u>Storage</u></li> <li>• <u>Research Record</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR11</li> <li>• 21CFR50.25</li> <li>• Federal Privacy Act</li> <li>• FDA Guidance: E6 GCP, Sections 4.6.5, 4.6.6</li> <li>• DAIDS Policy</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> </ul>
<b>Consult Notes</b>	
Requirement	<p>Chart note or other summary inserted into a subject's research record must contain:</p> <ul style="list-style-type: none"> <li>• Subject identifier</li> <li>• Signature and date by responsible clinician (may be electronic if computer generated)</li> </ul>
Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Chart Notes</u></li> <li>• <u>Copies</u></li> <li>• <u>Electronic signatures</u></li> <li>• <u>Identifiers</u></li> <li>• <u>Computer Records</u></li> </ul>
<b>Contraception: protocol-required</b>	
Requirement	<p>Vaccine and Prevention clinical trial sites:</p> <ul style="list-style-type: none"> <li>• Protocol required subject counseling on use of appropriate contraception must be documented prior to randomization/enrollment by one of the following:             <ol style="list-style-type: none"> <li>1. Chart note with documentation to support the protocol defined entry criteria for contraception.</li> <li>2. Completed Eligibility Checklist used as source documentation to support the protocol defined entry criteria for contraception. The Eligibility Checklist must correspond with the protocol text.</li> </ol> </li> <li>• If the protocol specifies that the subject must agree to practice 1 (one) or more forms of contraception, document one of the following:             <ol style="list-style-type: none"> <li>1. The methods the subject chooses to use.</li> <li>2. Subject counseling which included all of the following information:                 <ul style="list-style-type: none"> <li>➢ The number of forms of contraception that are necessary;</li> <li>➢ A list of acceptable forms of contraception was given to the subject;</li> <li>➢ The subject agreed to use contraception when necessary.</li> </ul> </li> <li>3. Subject-reported history of menopause or sterilization (hysterectomy, oophorectomy, tubal ligation, or vasectomy).</li> </ol> </li> </ul>

	<p>Therapeutic clinical trial sites:</p> <ul style="list-style-type: none"> <li>• Protocol required subject counseling on use of appropriate contraception must be documented prior to randomization/enrollment by one of the following:             <ol style="list-style-type: none"> <li>1. Chart note with documentation to support the protocol defined entry criteria for contraception.</li> <li>2. Completed Eligibility Checklist used as source documentation to support the protocol defined entry criteria for contraception. The Eligibility Checklist must correspond with the protocol text.</li> </ol> </li> <li>• If the protocol specifies that the subject must agree to practice 1 (one) or more forms of contraception, document either of the following:             <ol style="list-style-type: none"> <li>1. The methods the subject chooses to use.</li> <li>2. Subject counseling which included all of the following information:                 <ul style="list-style-type: none"> <li>➤ The number of forms of contraception that are necessary;</li> <li>➤ A list of acceptable forms of contraception was given to the subject;</li> <li>➤ The subject agreed to use contraception when necessary.</li> </ul> </li> <li>3. Acceptable documentation of menopause or sterilization (hysterectomy, oophorectomy, tubal ligation, or vasectomy) as specified in the protocol.                 <ul style="list-style-type: none"> <li>➤ Refer to the DAIDS TRP policy: "Guidance for Selecting and Modifying the Appropriate Protocol Eligibility Criteria Template for Pregnancy Prevention" for detailed information if not specified in the protocol.</li> </ul> </li> </ol> </li> <li>• Acceptable documentation to indicate that a child does not have reproductive potential:             <ol style="list-style-type: none"> <li>1. Determine if onset of menses (in girls) or onset of puberty (in boys) has occurred:                 <ul style="list-style-type: none"> <li>➤ Subject/caregiver history</li> <li>➤ Physical examination</li> </ul> </li> <li>2. If the subject is pre-pubescent:                 <ul style="list-style-type: none"> <li>➤ Document assessment and that the subject has not yet reached reproductive potential.</li> <li>➤ Contraceptive counseling and pregnancy testing are not necessary.</li> </ul> </li> <li>3. If the subject has started menstruation—regardless of age—contraception counseling and pregnancy testing are required as specified by the protocol.</li> </ol> </li> </ul>
<p>Suggestions</p>	<ul style="list-style-type: none"> <li>• The research clinician is responsible for providing the subject with information about the importance of using contraception as per the protocol; and then documenting that counseling occurred.             <ol style="list-style-type: none"> <li>1. It doesn't matter if the subject is heterosexual, homosexual, or abstinent. It may be helpful to stress:                 <ul style="list-style-type: none"> <li>➤ The importance of the requirement is due to the risk to the unborn.</li> <li>➤ That the research staff cannot make assumptions about the subject's sexual activities or interest in parenting a child.</li> </ul> </li> <li>2. The important factor is whether or not the subject is physically capable of fathering a child or becoming pregnant—regardless of age. This also applies to the pediatric/adolescent population.                 <ul style="list-style-type: none"> <li>➤ If the subject is, then the research clinician needs to document:                     <ul style="list-style-type: none"> <li>✓ The subject has been counseled regarding birth control/prevention of pregnancy as per protocol</li> <li>✓ The subject agrees to follow those requirements when necessary.</li> </ul> </li> <li>➤ If the subject is NOT physically capable, then the research clinician needs to document why.</li> </ul> </li> </ol> </li> <li>• This source documentation is in addition to the signed informed consent that acknowledges any such requirements.</li> <li>• The DAIDS Therapeutic Research Program (TRP) policy does not address pregnancy prevention from the pediatric perspective of when to start documenting this information for younger subjects; however, it is important for site staff to be attentive to the following:             <ol style="list-style-type: none"> <li>1. Subjects that have entered puberty are physically able to become pregnant/father a child.</li> <li>2. Preteens/teens may be sexually active without the knowledge of their parents/guardian.</li> <li>3. Site staff need to document their assessment of puberty onset.</li> <li>4. Monitors cannot assume contraceptive counseling and pregnancy tests aren't applicable if there is no documentation in the research record to indicate whether or not the onset of puberty has occurred.</li> </ol> </li> </ul>

	<p>5. Such documentation is not expected for very young children; however, site staff are expected to assess pre-pubescent subjects and not just base their judgment of reproductive potential solely on the subject's age.</p>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 50.25</li> <li>• 45 CFR 46</li> <li>• DAIDS TRP policy: "Guidance for Selecting and Modifying the Appropriate Protocol Eligibility Criteria Template for Pregnancy Prevention", May 17, 2000.</li> </ul>
<p><b>Copies: certified</b></p>	
Requirement	<ul style="list-style-type: none"> <li>• A copy-used as a source document should be certified that it was verified to be an exact copy of the original, having all of the same attributes and information as the original.             <ol style="list-style-type: none"> <li>1. This provides an audit trail in the event that the copy appears to have been altered.</li> <li>2. This is strongly recommended to comply with FDA Guidance; however, it is not required by regulation.</li> </ol> </li> <li>• If the original document is retained elsewhere, the copy does NOT need to be certified (e.g., original lab results are filed in the laboratory).</li> <li>• Monitors and FDA auditors may request to see the original documents or certified copies to verify validity of data for trial related monitoring.</li> <li>• Certification of a copy may be indicated by any of the following methods:             <ol style="list-style-type: none"> <li>1. A signed/initialed and dated statement on the copy that indicates it is an <i>exact copy of the original information</i>.                 <ul style="list-style-type: none"> <li>➢ This is to be done by the person making the copy, or, the person verifying that the copy is the same as the original.</li> <li>➢ The statement may be in the form of a stamp as long as it is accompanied by an original signature/initials and date.</li> </ul> </li> <li>2. Signature/initials and date without a statement.                 <ul style="list-style-type: none"> <li>➢ The dated signature/initials means that the signer has verified that the copy is an exact copy of the original.</li> </ul> </li> <li>3. Certification for copies received from an outside institution indicates it is an <i>unaltered copy as received</i>.</li> </ol> </li> <li>• Documentation received via fax are NOT considered to be originals.</li> <li>• Printouts retrieved from an institution's computer system ARE copies if the electronic file is the original source document.</li> <li>• Documents consisting of more than one page may be verified in a package as being one (1) copy if the package of copies is to remain intact in the file.             <ol style="list-style-type: none"> <li>1. For verification, the first page of the copy must have on it a signed and dated statement that indicates <i>the package consisting of X (specify) number of pages is an exact copy of the original information</i>.</li> <li>2. Each page must then be initialed and dated to verify that it is part of the package.</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Monitors may occasionally request to see the original documents during routine monitoring to verify their existence—it does not mean that alterations or fraud is suspected.</li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <a href="#">Computer Records</a></li> <li>• <a href="#">Initials</a></li> <li>• <a href="#">Research Record</a></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 11</li> <li>• FDA Guidance: E6 GCP, Section 1.51</li> <li>• FDA Guidance: Computerized Systems used in Clinical Trials (CSCT)</li> </ul>

<b>Death</b>	
Requirement	<ul style="list-style-type: none"> <li>• Document by one of the following:               <ol style="list-style-type: none"> <li>1. Obituary</li> <li>2. Autopsy report</li> <li>3. Death certificate</li> <li>4. Contact report documenting verbal communication with subject's healthcare provider, family member, significant other, friend, etc.</li> </ol> </li> <li>• If the death is reported via verbal communication, the following must be recorded in the source document to substantiate the date reported cause of death:               <ol style="list-style-type: none"> <li>1. Name of person reporting death and his/her relationship to subject</li> <li>2. Date death reported to site</li> <li>3. Date of death</li> <li>4. Reported cause of death</li> <li>5. Dates and methods site attempted to obtain official documentation to verify the verbal report of the date and cause of death</li> </ol> </li> <li>• SAE reporting according to DAIDS requirements.</li> </ul>
Suggestions	Official documentation is preferred and includes an autopsy report or death certificate. A copy of the document is to be included in the subject's file for verification of the date and cause of death.
Reference	<ul style="list-style-type: none"> <li>• 21CFR312.62(b)</li> <li>• <b>45CRF46.103(b)</b></li> <li>• FDA Guidance: E6 GCP, Sections 1.52, 8.3.11, 8.3.16</li> <li>• DAIDS SAE Reporting Manual</li> <li>• DAIDS Policy for SAE Reporting on Non-IND Studies</li> </ul>
<b>Departures / Deviations / Violations</b>	
Requirement	<ul style="list-style-type: none"> <li>• All protocol departures/deviations/violations must be recorded in the subject's research record.</li> <li>• If pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation.</li> <li>• Refer to local IRB/IEC/institution policies for reporting protocol departures to the IRB/IEC.</li> <li>• Examples of departures:               <ol style="list-style-type: none"> <li>1. A missed visit needs a note stating it is a missed visit and the site's attempts to locate the subject to request that he/she come in to make up that visit.</li> <li>2. Departures from protocol also include incomplete laboratory evaluations, physical assessments, questionnaires, etc.</li> <li>3. Changes in procedures or medication based on clinical judgment need a note explaining the problem, what was done, communications with the protocol team and IRB/IEC if necessary, actions, and resolution. An AER may need to be filed.</li> </ol> </li> </ul>
Suggestions	If the vital status of a subject is known during the time period that a visit was missed, that information and the means by which it was obtained (e.g., telephone contact, conversation with relative, or other medical records, etc.) should be reflected in the subject's research record.
Reference	<ul style="list-style-type: none"> <li>• 21CFR312.53(c)</li> <li>• 21CFR312.60</li> <li>• FDA Guidance: E6 GCP, Section 4.5.2 and 5.18.4</li> <li>• FDA Guideline for the Monitoring of Clinical Investigations: Part D and Part E</li> </ul>

## Documentation Standards

Requirement	<ul style="list-style-type: none"> <li>• All research personnel must comply with applicable standards for medical documentation as determined by their institutional policy, professional Code of Ethics, and licensing authority.</li> <li>• At a minimum, the following general standards must be followed:             <ol style="list-style-type: none"> <li>1. Keep handwritten notes and signatures legible (if necessary, print name underneath the signature).</li> <li>2. Sign and date all entries. Include credentials if required by the institution.</li> <li>3. Make error corrections in the following manner: draw a single line through the incorrect information, initial, date, and state reason for change (if necessary).</li> <li>4. Never obliterate entries that require correction.</li> <li>5. Never destroy original documents if they require error correction.</li> <li>6. Keep subject records secure yet accessible.</li> <li>7. Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries).</li> <li>8. Only use dark ink.</li> <li>9. Never use whiteout.</li> <li>10. Never use pencils.</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Hospital records used to substantiate data must meet institutional policy and are not held to GCP standards as are research records.</li> <li>• Records should be maintained chronologically.</li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <a href="#">Addenda</a></li> <li>• <a href="#">Error Corrections</a></li> <li>• <a href="#">Identifiers</a></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312.57</li> <li>• 21 CFR 312.58</li> <li>• 21 CFR 312.62</li> <li>• 21 CFR 312.68</li> <li>• FDA Guidance: E6 GCP, Sections 2.1, 4.5.2, 4.5.3, 4.9.1, 4.9.2, 4.9.3, 8.3.13, 8.3.14, and 8.3.15</li> <li>• FDA Guideline for the Monitoring of Clinical Investigations: Part E</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> </ul>
<h2>Endpoints</h2>	
Requirement	<ul style="list-style-type: none"> <li>• For study defined clinical or laboratory-based endpoints, the subject's research record must document the specifics of the event(s) or test result(s) as required by the protocol.</li> <li>• Results of all diagnostic evaluations needed to substantiate the diagnosis must be included in the subject's research records.</li> <li>• Document endpoints by any of the following examples, as applicable to the type of endpoint (e.g., clinical or laboratory):             <ol style="list-style-type: none"> <li>1. Chart note</li> <li>2. Consult note</li> <li>3. CRF used as a source document</li> <li>4. Documentation of death</li> <li>5. Radiology diagnostic interpretation</li> <li>6. Laboratory report.</li> <li>7. Paper copy of electronic report.</li> <li>8. Hard/fax copy lab report from research/ commercial lab.</li> <li>9. Hard/fax copy of correspondence from protocol team member (e.g., email from Data Manager) that subject has reached a study-defined lab based endpoint.</li> </ol> </li> </ul>

Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Copies</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Electronic Data</u></li> <li>• <u>Identifiers</u></li> <li>• <u>Lab Tests</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Sections 6.4 and 6.7</li> </ul>
<b>Entry Criteria (Inclusion / Exclusion Criteria)</b>	
Requirement	<ul style="list-style-type: none"> <li>• Documentation to address each of the protocol's inclusion and exclusion criteria must be present in the research record. <ol style="list-style-type: none"> <li>1. Chart notes to address the entry criteria.</li> <li>2. Eligibility checklists used as source documentation as long as the criteria included corresponds with the protocol and each inclusion/exclusion criterion is addressed.</li> <li>3. Original documents or certified copies of protocol required diagnostic results and/or history (e.g., laboratory results, radiology report, medication history, etc.).</li> </ol> </li> <li>• Documentation to address pertinent negatives must also be present in the research record. For example, exclusion criteria may require that the subject not be using any concomitant medications, or has not been diagnosed with any of a list of diseases. <ol style="list-style-type: none"> <li>1. Chart notes to address each negative criterion. For example, "None of the concomitant medications excluded by the protocol are being used by the subject" is an acceptable way to document that the criterion has been met.</li> <li>2. Eligibility checklists used as source documentation as long as the criteria included corresponds with the protocol and each inclusion/exclusion criterion is addressed.</li> <li>3. A blanket statement regarding <u>all</u> such exclusion criteria, such as "The subject does not meet any of the exclusion criteria outlined in the protocol" is NOT considered adequate.</li> </ol> </li> </ul>
Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Chart Note</u></li> <li>• <u>Contraception</u></li> <li>• <u>Copies</u></li> <li>• <u>Exemptions</u></li> <li>• <u>Karnofsky Score</u></li> <li>• <u>Medical History</u></li> <li>• <u>Medication History</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Sections 4, 5.18.4, 6.5</li> </ul>
<b>Error Corrections</b>	
Requirement	<ul style="list-style-type: none"> <li>• Error corrections must be done as follows: <ol style="list-style-type: none"> <li>1. Draw a single line through the incorrect information.</li> <li>2. Initial, date, and state reason for change (if necessary).</li> <li>3. Insert the correction.</li> </ol> </li> <li>• Never use pencil to write entries.</li> <li>• Never use "white-out".</li> <li>• Never obliterate entries that require correction.</li> <li>• Never destroy original documents, even if they require error correction.</li> <li>• Do not alter past-dated notes, chart notes/progress notes (e.g., by writing alongside or adding to prior entries).</li> </ul>

	<ul style="list-style-type: none"> <li>• Error corrections that are not done according to procedure will result in inadequate source documentation.</li> </ul>
Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Addenda</u></li> <li>• <u>Chart Note</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Initials</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Sections 4.9 and 5.18.4</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> </ul>

**Flow Sheets**

Requirement	<ul style="list-style-type: none"> <li>• Flow sheets to be used as source documentation must be:             <ol style="list-style-type: none"> <li>1. Signed/initialed and dated by the clinician responsible for the entry.</li> <li>2. Labeled with an appropriate subject identifier.</li> </ol> </li> <li>• If more than one person makes entries on a flow sheet, each entry must be signed/initialed and dated.</li> <li>• Entries for timed serial evaluations (e.g., vital signs, pharmacokinetic studies, etc.) must also note times if required by the protocol.</li> </ul>
Suggestions	<p>Examples of flow sheets:</p> <ul style="list-style-type: none"> <li>• Pharmacokinetic flow sheets</li> <li>• Vital signs flow sheets</li> <li>• Weight/anthropometric data</li> <li>• Medication logs</li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Chart Note</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Identifiers</u></li> <li>• <u>Initials</u></li> <li>• <u>Source Documentation</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Sections 4.9 and 5.18.4</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> </ul>

**Identifiers**

Requirement	<ul style="list-style-type: none"> <li>• All source documents must be consistently labeled with at least 1 (one) unique identifier so monitors can verify that documents correspond to particular subjects.</li> <li>• Examples of unique identifiers:             <ol style="list-style-type: none"> <li>1. Hospital identification number</li> <li>2. Medical record number</li> <li>3. Social Security Number</li> <li>4. Patient identification (PID) number</li> <li>5. Full name if there are no other subjects with that name at the site</li> <li>6. Two non-unique identifiers in combination</li> </ol> </li> <li>• Identifiers that are NOT unique:             <ol style="list-style-type: none"> <li>1. Date of birth</li> </ol> </li> </ul>
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	<ul style="list-style-type: none"> <li>2. Subject initials</li> <li>3. Full name if there are other subjects with that name at the site</li> <li>• Identifiers on original documents must NEVER be obliterated, even if a new identifier is added to the document (e.g., placing a PID label over a subject's name).</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• COPIES of original records may have PID/SID numbers obliterated and replaced with an acceptable identifier if records containing such numbers are to be viewed by non-research staff.               <ol style="list-style-type: none"> <li>1. The change must be dated and initialed.</li> <li>2. ORIGINAL source documents must NEVER be modified in this way.</li> <li>3. Monitors must have access to the original documents for review.</li> </ol> </li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Confidentiality</u></li> <li>• <u>Documentation Standards</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Section 5.5.5</li> </ul>

**Informed Consent**

Requirement	<ul style="list-style-type: none"> <li>• Informed consent must be documented by the use of a written consent form:           <ol style="list-style-type: none"> <li>1. Except if the IRB has waived the requirement for a signed written consent form in accordance with the requirements of 45CFR46.117(c) and 21CFR56.109(c).               <ul style="list-style-type: none"> <li>➤ Documentation of the IRB's decision to waive the requirement for written consent must be present in the regulatory files at the site.</li> </ul> </li> <li>2. All consent forms must be approved by the local IRB/IEC.</li> <li>3. All consent forms must be submitted to DAIDS for review.</li> <li>4. All consent forms for new protocols and amendments must be approved by DAIDS.</li> <li>5. Protocol-specific consent must be obtained prior to randomizing/enrolling a subject.</li> </ol> </li> <li>• Signatures on the consent form:           <ol style="list-style-type: none"> <li>1. Must be legal name and may not include fabricated/falsified names.</li> <li>2. Must not use an initial for the last name.</li> <li>3. Strongly recommend not using an initial for the first name; however, if the person commonly signs his/her name using an initial for the first name, it will be accepted as long as it is also acceptable as per the policy of the institution.</li> <li>4. Must be in ink.</li> <li>5. Must be dated by each person signing the form. It is NOT acceptable for research staff to complete the date for another signer.</li> </ol> </li> <li>• Federal regulations and institutional policy must be followed when screening subjects to determine potential eligibility.           <ol style="list-style-type: none"> <li>1. Screening is defined as any procedure done solely for the purpose of determining a potential study subject's eligibility or to enter a subject into a research study.</li> <li>2. Consent must be obtained before invasive procedures are performed.</li> <li>3. It is required unless the IRB has waived the requirement for a signed written consent form as per the requirements of 21CFR56.109(c).               <ul style="list-style-type: none"> <li>➤ Documentation of the IRB's decision to waive the requirement for written consent must be present in the regulatory files at the site.</li> </ul> </li> <li>4. Either an IRB/IEC approved generic screening consent form or the IRB/IEC approved protocol consent form is acceptable.</li> <li>5. If a site customarily uses IRB/IEC approved screening consents for all study subjects, or for all subjects screened for certain protocols:               <ul style="list-style-type: none"> <li>➤ The screening consent must be signed &amp; dated before screening for protocol eligibility begins.</li> <li>➤ The protocol-specific consent must be signed &amp; dated before randomization/enrollment into the protocol.</li> </ul> </li> </ol> </li> </ul>
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6. Access, and consent for access, to medical records and/or databases for use in identifying potentially eligible study subjects is dependant upon the policies of the local institution/IRB/IEC.
  - Review of medical records and/or databases outside of your institution is NOT permitted without the prior consent of the potential study subjects.
7. Maintain a list/log of subjects screened for a protocol.
  - It is not required to include broad medical records/database reviews; however, it would be good practice to include those subjects for verification that there was no bias in the selection of potential subjects.
- Information given to the subject or the representative must be in a language they can understand.
  1. When the study subject population includes non-English speaking people so that the clinical investigator or the IRB/IEC anticipates that the consent interviews are likely to be conducted in a language other than English.
  2. IRB/IEC approved translated consent form.
  3. A consultant may be utilized to assure that the translation is correct.
  4. A copy of the translated consent document must be given to each appropriate subject.
  5. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may NOT be substituted for a written translation.
  6. If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation.
    - Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists.
    - If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective.
    - If investigators enroll subjects without an IRB/IEC approved written translation, a "short form" written consent document, in a language the subject understands, should be used to document the elements of informed consent.
    - Requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed if a short form is used. Refer to the provisions of 45 CFR 46.116, 46.117 and 21 CFR 50.25, 50.27(b)(2).
    - Financial burden to the institute/IRB/IEC is NOT an acceptable reason for lack of translated consent forms and non-compliance with the Federal regulations.
- Illiterate persons who understand English may have the consent read to them and "make their mark" if appropriate under applicable state law.
  1. Investigators should be cautious when enrolling subjects who may not truly understand what they have agreed to do.
  2. The IRB/IEC should consider illiterate persons as likely to be vulnerable to coercion and undue influence and should determine that appropriate additional safeguards are in place when enrollment of such persons is anticipated.
  3. Requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed, if a short form is used. Refer to the provisions of 45CFR46.116, 46.117 and 21 CFR 50.25, 50.27(b)(2).
- Refer to 45CFR46 for special requirements of obtaining the informed consent of special populations in research.
  1. Prisoners
  2. Pregnant women, fetuses (perinatal studies)
  3. Children
    - Sites must obtain proof of guardianship before screening the subject for protocol enrollment if it is not clearly documented whom the subject's the legal guardian is. For example, chart notes from previous medical care indicates parent provided consent for treatment in the past, but now a different relative is caring for the subject.
  4. Wards of the state and/or foster children
  5. IRB/IEC may waive the requirement for parental consent of adolescents as per the requirements of 45CFR46.408(c) if within state law.
    - Documentation of the IRB's decision to waive the requirement for parental consent must be present in the regulatory files at the site.
- If a revised informed consent form is required, it must be obtained as soon as possible.
- Additional documentation of the informed consent process and obtaining informed consent may be necessary as per local IRB/IEC or institution policy.

<p>Suggestions</p>	<ul style="list-style-type: none"> <li>• Signatures on the consent form may include the person who conducted the consent process, a witness to the consent process, translator, or others according to the requirements of the local IRB/IEC.</li> <li>• It is acceptable for sites to maintain consents in a file separate from a subject's research record, provided the site does this consistently for all subjects enrolled in the study and maintains any updated versions of the signed consents in the same manner.</li> <li>• The process of obtaining informed consent should be documented in the research record in addition to obtaining a signed informed consent form.</li> <li>• The following should be documented:             <ol style="list-style-type: none"> <li>1. The date and time. A notation of the time is especially important when consent is obtained the same day that randomization/enrollment occurs.</li> <li>2. A description of the consent process to substantiate that it was not coercive.</li> <li>3. Information about the study, including all available options, was provided in a language understood by the subject.</li> <li>4. The subject was given adequate opportunity to consider all available options.</li> <li>5. The subject's questions were answered.</li> <li>6. The subject's comprehension of the information.</li> </ol> </li> <li>• It is strongly recommended that this additional documentation be performed.</li> <li>• Options for documentation in the research record:             <ol style="list-style-type: none"> <li>1. Use forms, templates, quizzes, etc. to facilitate documentation.</li> <li>2. Create a detailed informed consent checklist incorporating the items above and use this to document the process.                 <ul style="list-style-type: none"> <li>➤ This would need to be signed and dated by the person obtaining the informed consent.</li> </ul> </li> <li>3. The person obtaining the informed consent could write a comprehensive progress note that covers the items listed above.</li> <li>4. Have the process documented, in detail, in a Standard Operating Procedure.                 <ul style="list-style-type: none"> <li>➤ The person obtaining the informed consent could document in the patient's chart that the informed consent was obtained per SOP.</li> <li>➤ A copy of the SOP should be kept in a central regulatory file.</li> </ul> </li> </ol> </li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Assent</u></li> <li>• <u>Confidentiality</u></li> </ul>
<p>Reference</p>	<ul style="list-style-type: none"> <li>• 45CFR46</li> <li>• 45CFR46.117(c)</li> <li>• 45CFR46.408(c)</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• 21CFR56.109(c)</li> <li>• 21CFR312.62</li> <li>• FDA Guidance: E6 GCP, Sections 4.8, 8.3.12, 8.2.3, 8.3.2</li> <li>• FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, Q&amp;A Nos. 40, 41, 51, and Page 5.</li> <li>• OHRP Guidance: Informed Consent, Non-English Speakers, November 1995</li> <li>• DAIDS Protocol Registration Policy and Procedure Manual</li> <li>• DAIDS SOP: Essential Documents</li> </ul>
<p><b>Initials</b></p>	
<p>Requirement</p>	<p>Initials may be used in place of signatures provided that a signature key inclusive of the following is maintained at the site or on the document itself:</p> <ul style="list-style-type: none"> <li>• Initials</li> <li>• Signature</li> <li>• Credentials (if applicable)</li> </ul>

Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Section 8.3.24</li> <li>• Thompson Publishing Group's <i>Guide to Good Clinical Practice</i>, Sections 210, 300, 410</li> <li>• DAIDS Essential Documents SOP</li> </ul>
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### **Karnofsky Score**

Requirement	<ul style="list-style-type: none"> <li>• Record in the research record the actual score assigned to a subject at a given point in time (as specified in the protocol).</li> <li>• Provide documentation as per protocol requirements.</li> </ul>
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Suggestions	Data to support the assigned score is usually obvious upon reviewing the subject's medical record; if it is not, then rationale for the score should be noted.
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Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Section 4</li> </ul>
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### **Lab Tests: Specimen Collection (Research and Routine)**

Requirement	<ul style="list-style-type: none"> <li>• Document that specimens were obtained as required by the protocol.</li> <li>• If required by the protocol, specimen collection time must be noted.</li> <li>• If fasting is required by the protocol, confirmation by subject of fasting more than 8 (eight) hours, or as specified by the protocol, must be noted. Some protocols may require that the specific date and time of the last food/fluids are recorded.</li> </ul>
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Suggestions	<p>It is acceptable to write a note that broadly indicates that specimens were obtained for the protocol required tests.</p> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Case Report Forms</u></li> <li>• <u>Computer Records</u></li> <li>• <u>Copies</u></li> </ul>
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Reference	<ul style="list-style-type: none"> <li>• 21CFR11 subpart C</li> <li>• FDA Guidance: E6 GCP, Section 4, 8.3.25</li> <li>• FDA Guidance: Computerized Systems Used in Clinical Trials, Parts III and IV</li> </ul>
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### **Lab tests: Results (Research and Routine)**

Requirement	<ul style="list-style-type: none"> <li>• All reports must have appropriate subject identifiers and date of specimen collection.</li> <li>• Lab reports must identify where the test was performed.</li> <li>• When reporting lymphocyte counts/percentages, a notation of the corresponding CBC with differential to verify total lymphocyte count may be required, depending on the lab's reporting format.</li> <li>• For batched and/or blinded research lab analyses, no documentation of results is required in the subject's research record unless the <input type="checkbox"/>blinded results were disclosed to the site for the purposes of subject management, study termination, or re-randomization/step assignment.</li> </ul>
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Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Case Report Forms</u></li> <li>• <u>Computer Records</u></li> <li>• <u>Copies</u></li> <li>• <u>Endpoints</u></li> <li>• <u>Identifiers</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR11, Subpart C</li> <li>• FDA Guidance: E6 GCP, Sections 4, 8.2.11</li> <li>• FDA Guidance: Computerized Systems Used in Clinical Trials, Part IV</li> </ul>

**Medical History: General and HIV-specific**

Requirement	<ul style="list-style-type: none"> <li>• Written documentation of medical history as defined by protocol. Including, <i>but not limited to</i>, diagnoses, signs/symptoms, medications, tests.</li> <li>• Verbal history, recorded in research record, is acceptable. Note the source (person providing history).</li> <li>• Chart note or referring healthcare provider's letter is acceptable.</li> <li>• Obtain reports of laboratory tests, diagnostic procedures, and examinations as necessary to substantiate history.</li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR312.62</li> <li>• FDA Guidance: E6 GCP, Sections 2.11, 4</li> </ul>

**Medical Records**

Requirement	<ul style="list-style-type: none"> <li>• Review of medical records is necessary to extract all information that may be relevant to the protocol. <ol style="list-style-type: none"> <li>1. Monitors and FDA auditors may request to see original documents or certified copies to verify validity of data for trial related monitoring.</li> <li>2. The following are examples of data: physical exams, concomitant medications, signs and symptoms/adverse events, diagnoses, laboratory results, diagnostic reports, etc.</li> </ol> </li> <li>• Medical records at institutions with primary care facilities: <ol style="list-style-type: none"> <li>1. All records including the subject's primary care chart must be accessible to the monitor for review/audits.</li> <li>2. Note if records are missing and efforts to locate them.</li> </ol> </li> <li>• Medical records from outside institutions and primary care providers: <ol style="list-style-type: none"> <li>1. Records sent from other treating facilities that are incorporated into the subject's research record.</li> <li>2. Monitors and FDA auditors may request to see original documents or certified copies to verify validity of data for trial related monitoring.</li> <li>3. Subject must sign a release form if needed.</li> <li>4. Unique identifier.</li> <li>5. Record in the research record efforts to obtain outside medical records as needed for protocol participation.</li> <li>6. Notations of follow-up efforts for records requested but not received.</li> </ol> </li> <li>• Monitors must have access to the source documents located in these records during audits.</li> </ul>
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Suggestions	<ul style="list-style-type: none"> <li>• Sites should document all attempts to secure records pertaining to the subject while on-study that are required for, or are considered relevant to, the subject's study participation.</li> <li>• Sites should acknowledge (record in research record) when medical records are missing despite efforts to obtain them.</li> <li>• Sometimes it is impossible for a site to obtain copies of medical records while a subject is on-study. <ol style="list-style-type: none"> <li>1. This may occur, for example, when a research subject is seen in an out-of-town clinic or hospital, and the site is unable to persuade the outside facility to send copies of pertinent treatment records despite signed release of study subject.</li> <li>2. In this case, site personnel are to include in the research record an acknowledgment that certain medical records are missing and the site's efforts to obtain them.</li> </ol> </li> </ul> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Computer Records</u></li> <li>• <u>Confidentiality</u></li> <li>• <u>Copies</u></li> <li>• <u>Identifiers</u></li> <li>• <u>Research Record</u></li> <li>• <u>Source Documentation</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312.62</li> <li>• FDA Guidance: E6 GCP, Sections 1.21, 1.22, 1.23, 1.24, 1.51, 1.52, 1.58, 2.10, 2.11, 4, 5.5.5</li> </ul>
<b>Prescriber</b>	
Requirement	<p>Investigational agents are dispensed only upon the written order of the Investigator of Record (IOR) or upon the order of a licensed practitioner directly responsible to the IOR as stated on the Form FDA 1572 (IND studies) or the authorized prescribers list (non-IND studies).</p> <ul style="list-style-type: none"> <li>• Prescriptions shall be written with ink, indelible pencil, typewriter, or computer generated and shall be signed by the practitioner: <ol style="list-style-type: none"> <li>1. Manually/hand written or with an electronic signature.</li> <li>2. Signature stamps are NOT permitted.</li> <li>3. Signing blank prescription forms is NOT permitted.</li> <li>4. It is NOT permitted for an individual who is not an authorized prescriber to sign a prescription with an authorized prescriber's name and then add her/his own name to it in an effort to make it legal. For example, a nurse may not sign a doctor's name to a prescription and then add her/his name to it if she/he is not an authorized prescriber.</li> </ol> </li> <li>• By signing the Form FDA 1572, the IOR has certified that the investigational agent will be administered only to subjects under his/her personal supervision or under the supervision of subinvestigators responsible to him/her.</li> <li>• Only subinvestigators listed on the Form 1572 or authorized prescribers list may write orders for study products.</li> <li>• An agent for the IOR or subinvestigator may prepare prescriptions in advance for the SIGNATURE of a practitioner.</li> <li>• The prescribing practitioner is responsible in case the prescription does not conform in all essential aspects of the protocol, to the law and regulations.</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• The following is a test question to determine if an individual is authorized in that jurisdiction to write prescription for study drugs/agents: Can the prescriber sign a prescription for non-study medication that could legally be filled?</li> </ul> <p>Also refer to sections:</p> <ul style="list-style-type: none"> <li>• <u>Electronic Signatures</u></li> </ul>

	<ul style="list-style-type: none"> <li>• <u>Prescriptions</u></li> <li>• <u>Study Drug/Agent</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312.61</li> <li>• FDA Form 1572</li> <li>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups</li> </ul>
<b>Prescriptions</b>	
Requirement	<p>Documentation of Prescriptions for Study Drugs/Agents:</p> <ul style="list-style-type: none"> <li>• Chart note or flow sheet indicating prescription was written; OR, copies of the prescriptions that were sent to the pharmacy (investigational or commercial).             <ol style="list-style-type: none"> <li>1. Specify the study drug/agent, dose, schedule, and route of administration.</li> </ol> </li> <li>• All study prescriptions must be signed by a clinician authorized to prescribe in the site's jurisdiction who is listed on the current FDA Form 1572 (IND studies) or authorized prescribers list (non-IND studies) for a given protocol at the participating site.</li> <li>• Prescriptions must include:             <ol style="list-style-type: none"> <li>1. PID/SID numbers (subject's name instead if it is for a commercial pharmacy)</li> <li>2. Name of study agent</li> <li>3. Dose</li> <li>4. Schedule</li> <li>5. Route of administration, (or protocol number if that provides equivalent information)</li> <li>6. Number of dosing units to be dispensed, OR, instructions (e.g., sufficient supply until next visit) in place of an exact quantity.</li> </ol> </li> <li>• Prescriptions may be written with refills.</li> </ul> <p>Documentation of Changes in Study Treatment:</p> <ul style="list-style-type: none"> <li>• Any change in study drug/agent status must be documented with sufficient detail to support and provide an explanation for the change as recorded on the CRF.</li> <li>• Entries regarding dose modifications must include the reason for the change and the actual dosage change.</li> <li>• Notes regarding the holding of study drug/agent must include the reason for the hold.</li> <li>• Notes regarding the reinstatement of study drug/agent must include the reason for reinstatement of drug/agent and the dosage.</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Quantity or other dispensing instructions need to be specified on the prescription to prevent an open-ended supply of drug/agent from being dispensed.</li> <li>• DAIDS, as sponsor of a study, requires the pharmacists to keep records of the disposition of all study drugs/agents that are distributed from the NIAID CRPMC.</li> </ul> <p>Also refer to sections:</p> <ul style="list-style-type: none"> <li>• <u>Prescriber</u></li> <li>• <u>Study Drug/Agent</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Form 1572</li> <li>• 21 CFR 312.50, .57, .59, .61, .62</li> <li>• FDA Guidance: E6 GCP, Section 5.14</li> <li>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups</li> </ul>

**Procedures: Diagnostic, Therapeutic, Surgical, etc.**

Requirement	<p>As appropriate, results, interpretations and/or diagnostic procedures required by the protocol must be documented. For example:</p> <ul style="list-style-type: none"><li>• Chart note</li><li>• CRF used as a source document</li><li>• Report</li><li>• Flow sheet</li><li>• Monitors and FDA auditors may request to see the original document or certified copy to verify validity of data for trial related monitoring.</li></ul>
Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"><li>• <u>Chart Note</u></li><li>• <u>Computer Records</u></li><li>• <u>Documentation Standards</u></li><li>• <u>Error Correction</u></li><li>• <u>Identifiers</u></li><li>• <u>Medical Records</u></li></ul>
Reference	<ul style="list-style-type: none"><li>• 21CFR11</li><li>• 21CFR312</li><li>• FDA Guidance: E6 GCP, Section 4</li></ul>

**Questionnaires: Subject/guardian and/or study personnel completed**

Requirement	<ul style="list-style-type: none"><li>• The actual data on a subject/guardian completed questionnaire or CRF does not need supporting source documentation.</li><li>• Documentation is required is to show that the protocol required questionnaire was given to the subject/guardian in accordance with protocol requirements.<ol style="list-style-type: none"><li>1. For example:<ul style="list-style-type: none"><li>➢ Enter a note into the subject's chart indicating the questionnaire/form was given to the subject/guardian to complete on a specified date.</li><li>➢ Indicate on a checklist that the subject/guardian completed the specified form on a specified date.</li></ul></li><li>2. If the questionnaire is NOT completed by the subject, indicate who completed it and why.</li><li>3. If questions are completed by study personnel:<ul style="list-style-type: none"><li>➢ Those questions/sections must be signed/initialed and dated.</li><li>➢ Supporting documentation for data must be in the research record (when applicable).</li><li>➢ Note if the form was completed via study personnel interviewing the subject/guardian.</li><li>➢ This pertains ONLY to questions that are an actual part of the questionnaire/data, not information related to form keying or headers.</li></ul></li><li>4. Retain copy of questionnaire, form, or test as per the protocol.</li></ol></li></ul>
Suggestions	<p>Examples of questionnaires:</p> <ul style="list-style-type: none"><li>• Adherence</li><li>• Health Status</li><li>• Neuropsychology tests</li><li>• Nutrition surveys</li><li>• Quality of Life</li><li>• Patient logs</li><li>• Subject diaries</li></ul>

	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>CRFs used as Source Documentation</u></li> <li>• <u>Communications</u></li> <li>• <u>Confidentiality</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Initials</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Section 4</li> </ul>
<b>Research Record</b>	
Requirement	<ul style="list-style-type: none"> <li>• All documents that substantiate data collected and/or are relevant to a subject's participation in a clinical investigation constitute a research record. They include the following:             <ol style="list-style-type: none"> <li>1. Subject-signed informed consent</li> <li>2. Source documents</li> <li>3. Case history</li> <li>4. Investigational pharmacy records</li> <li>5. CRFs</li> </ol> </li> <li>• Individuals authorized to review the records may request to inspect any or all of the above types of documents.</li> <li>• Investigators are responsible for maintaining accurate and complete research records.</li> <li>• Each subject must consent in writing to direct access to his/her research record, including original medical records held by the institution conducting the research, for trial-related monitoring, audit, IRB review, and regulatory inspection by authorized individuals.</li> <li>• Sites must be able to produce a research record in its entirety for monitoring and/or audit.             <ol style="list-style-type: none"> <li>1. Sites must provide direct access to each subject's research records, including the entire medical record held by the institution conducting the research.</li> <li>2. Direct access to all records held at the institution is necessary for purposes of identifying and monitoring trial-related and/or pertinent data (e.g., medical history, contraindications for enrollment, adverse experiences, etc.) in the source documents.</li> <li>3. The source of study data must be verifiable in original source documents or certified copies.</li> </ol> </li> <li>• Shadow files are an adjunct to the subject's medical record or clinic chart.             <ol style="list-style-type: none"> <li>1. These files, consisting of copied source documents, are intended to reflect a subject's complete, study specific record.</li> <li>2. Copied documents in these files are NOT the original source documents.</li> <li>3. Monitors and FDA auditors may request to see the original documents or certified copies to verify validity of data for trial related monitoring.                 <ul style="list-style-type: none"> <li>➤ If the site is not able to produce original source documents or certified copies during a monitoring review, the data will be considered as having inadequate source documentation.</li> </ul> </li> <li>4. May include protocol required documentation such as the following examples:                 <ul style="list-style-type: none"> <li>➤ Informed consent</li> <li>➤ Screening results</li> <li>➤ Baseline events</li> <li>➤ Vital status</li> <li>➤ Clinical and laboratory findings</li> <li>➤ Management of study drugs/agents and toxicities</li> </ul> </li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Original records are ideal but shadow files are acceptable. Monitors may occasionally request to see the original documents during routine monitoring to verify their existence—it does not mean that alterations or fraud is suspected.</li> <li>• Hospital records used to substantiate data must meet institutional policy and will not be monitored for adherence to the GCP standards that research-specific records are required to follow.</li> </ul>

	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Confidentiality</u></li> <li>• <u>Copies</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Identifiers</u></li> <li>• <u>Source Document</u></li> <li>• <u>Storage</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312</li> <li>• 45 CFR 46</li> <li>• FDA Guidance: E6 GCP, Sections 4.9, 5.15, 6.10, 7, and 8</li> </ul>
<b>Source Document</b>	
Requirement	<ul style="list-style-type: none"> <li>• Any original documents or certified copies that include documentation pertaining to the subject's condition while on a research study. This includes <i>but is not limited to</i> the following:             <ol style="list-style-type: none"> <li>1. Medical record</li> <li>2. Clinic chart</li> <li>3. CRFs used as source documents</li> <li>4. Primary care provider's office chart</li> <li>5. Laboratory reports and radiology reports</li> <li>6. Flow sheets, medication records, prescriptions, EKG tracings, etc.</li> </ol> </li> <li>• Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution must make available for direct access all requested documentation that may be relevant to the subject's trial participation. This includes CRFs and medical records.</li> <li>• If there is no supporting evidence to verify protocol-required data and procedures, source documentation will be considered inadequate.</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Source documents should contain at least the following:             <ol style="list-style-type: none"> <li>1. Medical History, including relevant history for the disease being treated.</li> <li>2. Current physical condition.</li> <li>3. Current illness and injuries.</li> <li>4. Current medications.</li> <li>5. Medications discontinued within the last month (or longer if required by protocol).</li> <li>6. Descriptions of the informed consent process.</li> <li>7. Dates of actual subject visits.</li> <li>8. Completion of study procedures (laboratory samples, X-rays, EKGs), including dates and results.</li> <li>9. Adverse experiences, illness, or problems reported by the subject during the course of the study.</li> <li>10. Deviations from the protocol and the reason.</li> <li>11. Unexpected occurrences/problems.</li> <li>12. Existing record of all study treatments.</li> <li>13. Any additional information required by the protocol.</li> </ol> </li> <li>• It is not the monitor's responsibility to search for source documents or to travel to another site to obtain access to research records.</li> <li>• When a source document is not in the research record, the monitor may ask the site staff if they can obtain the document during the course of the site visit. (e.g., a missing lab slip or a document that is temporarily in another department of the hospital.)             <ol style="list-style-type: none"> <li>1. The record will not be cited for inadequate source documentation if the missing document is provided to the monitor for review before completion of the site visit and it is found to be adequate.</li> <li>2. It is unacceptable for study personnel to submit missing documentation to a monitor between site visits.</li> </ol> </li> </ul>

	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Chart Notes</u></li> <li>• <u>Copies</u></li> <li>• <u>Informed Consent</u></li> <li>• <u>Medical Record</u></li> <li>• <u>Research Record</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR 312.62 (b), 312.68</li> <li>• FDA Guidance: E6 GCP, Sections 1.51, 1.52, 4.8.10 (n) 4.9.7, 4.9.5, 4.11.1, 5.18.1, 5.18.4, and 8.3.13</li> <li>• FDA Compliance Program Guidance Manual 7248.811</li> <li>• Thompson Publishing Group, <i>Guide To Good Clinical Practice</i>, Section 410</li> </ul>
<b>Storage of Source Documents</b>	
Requirement	<ul style="list-style-type: none"> <li>• Sites must retain research records according to Federal regulation, institutional policy, DAIDS SOP, the protocol, and/or Group SOPs. Includes:             <ol style="list-style-type: none"> <li>1. Source documents</li> <li>2. CRFs</li> <li>3. Pharmacy records</li> <li>4. Regulatory files</li> </ol> </li> <li>• For electronic data storage, the FDA expects to be able to reconstruct the study.             <ol style="list-style-type: none"> <li>1. This applies not only to the data, but also how the data were obtained and managed.</li> <li>2. All versions of application software, operating systems, and software development tools involved in processing of data or records need to be available as long as data or records associated with these versions are required to be retained.</li> <li>3. Records should be backed up regularly in a way that would prevent a catastrophic loss and ensure the quality and integrity of the data.                 <ul style="list-style-type: none"> <li>➤ Backup records should be stored in a secure location specified in the SOPs.</li> <li>➤ Storage needs to be separate from the original records, such as in a separate building or an off site facility.</li> <li>➤ Backup and recovery logs need to be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.</li> </ul> </li> </ol> </li> <li>• Refer to the separate DAIDS SOP, Storage of CRFs and Pharmacy Records, for the procedure on shipping CRFs to DAIDS for permanent storage.             <ol style="list-style-type: none"> <li>1. If CRFs are used as source documentation, submit copies of those CRFs to DAIDS for permanent storage.</li> <li>2. The site should then retain the original CRFs used as source documentation with the other source documents.</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• This SOP pertains to record storage within the institution.</li> <li>• CRFs are an adjunct to other source documents and may be filed with the source documents; however, it is recommended that source documents be stored separately from CRFs.             <ol style="list-style-type: none"> <li>1. Provides a safeguard against the simultaneous loss of both the source documents and the CRFs.</li> <li>2. Assists in maintaining subject confidentiality.</li> <li>3. If CRFs are used as source documentation:                 <ul style="list-style-type: none"> <li>➤ The original CRFs used as source documents should be filed with the other source documents.</li> <li>➤ Copies of those CRFs should then be filed with the other CRFs if in accordance with Group SOPs.</li> </ul> </li> </ol> </li> <li>• Sites may store copies of source documentation as computer records, microfiche or microfilm.             <ol style="list-style-type: none"> <li>1. Site personnel should verify the quality of the copies and certify them.</li> </ol> </li> </ul>

Suggestion  
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	<p>2. If applicable, the monitor must be given access to a computer system, microfiche/microfilm reader during his/her site visit to reviewed documents stored in this manner.</p> <p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Case Report Forms</u></li> <li>• <u>Computer Records</u></li> <li>• <u>Copies</u></li> <li>• <u>Electronic Signatures</u></li> <li>• <u>Source Document</u></li> </ul>
<p>Reference</p>	<ul style="list-style-type: none"> <li>• 21CFR11</li> <li>• 21CFR312.62</li> <li>• FDA Guidance: Computerized Systems Used In Clinical Trials, Sections VI, D and IX, C</li> <li>• DAIDS SOP: Storage of CRFs and Pharmacy Records</li> <li>• DAIDS SOP: CRF Destruction List</li> </ul>
<p><b>Study Drug / Agent</b></p>	
<p>Requirement</p>	<ul style="list-style-type: none"> <li>• Supplied study drugs/agents are dispensed only upon the written order of the Investigator of Record (IoR) or upon the order of a licensed practitioner directly responsible to the IoR as stated on the Form FDA 1572 (IND studies) or authorized prescribers list (non-IND studies).</li> <li>• Study drug/agent use by the subject must be recorded in the research record.</li> <li>• Medications that meet one or more of the following criteria for protocol-specified drugs/agents or non-specified drugs/agents are considered to be "study drugs/agents":             <ol style="list-style-type: none"> <li>1. Protocol-Specified Drugs/Agents                 <ul style="list-style-type: none"> <li>➤ Drugs/agents specified by name for use in the study. The following criteria apply:                     <ul style="list-style-type: none"> <li>✓ All drugs/agents distributed through NIAID's distribution center (CRPMC). (In rare instances this may not apply, and in that event, site staff will be notified.)</li> <li>✓ All drugs/agents that are specifically required by the protocol, including those that are individually specified or any that are chosen from a list of specified drugs/agents.</li> </ul> </li> <li>➤ Risks for each of these drugs/agents must be included in the informed consent form.</li> <li>➤ The protocol will specify whether SAE reporting is required and, if so, the intensity or level of AE reporting.</li> </ul> </li> <li>2. Non-Specified Drugs/Agents:                 <ul style="list-style-type: none"> <li>➤ In addition to any drugs/agents specifically named for use in a study, other drugs/agents that are being used to address the study's primary therapeutic objective(s) and any other study objective designated for this purpose by the protocol will be considered to be study drugs/agents.                     <ul style="list-style-type: none"> <li>✓ Includes drugs/agents that are not individually specified by name in the protocol nor distributed by the CRPMC. For example: GART/PART studies, treatment strategy studies, and long-term follow-up studies.</li> <li>✓ Protocols may designate distinct types or classes of drugs/agents that will or will not be "study drugs/agents".</li> </ul> </li> <li>➤ Risks of individual non-specified drugs/agents do not need to be included in the informed consent document; however, general statements regarding study treatment risk may need to be made. For example, including common risks for relevant drug classes or referral to package inserts/approved patient education material need to be considered.</li> <li>➤ The protocol will specify whether SAE reporting is required and, if so, the intensity or level of AE reporting. Unless the protocol gives further instructions, all drugs/agents meeting this definition must be taken into account in deciding the intensity of AE reporting and included in assessments concerning relationship of SAEs to "study drug/agent".</li> </ul> </li> <li>3. Some protocols may have BOTH "specified" and "non-specified" study drugs/agents.</li> </ol> </li> </ul>

Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Prescriber</u></li> <li>• <u>Prescriptions</u></li> <li>• <u>Pharmacy Accountability Records</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR312.32(c)</li> <li>• 21CFR312.64(b)</li> <li>• DAIDS Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Groups</li> <li>• DAIDS Serious Adverse Experience (SAE) Reporting Manual</li> </ul>

### **Study Drug / Agent Accountability**

Requirement	<ul style="list-style-type: none"> <li>• The Pharmacist of Record must keep records to account for the disposition of study drugs/agents by documenting the following:             <ol style="list-style-type: none"> <li>1. Shipment records</li> <li>2. Lot numbers</li> </ol> </li> <li>• Allows tracking of:             <ol style="list-style-type: none"> <li>1. Product lot numbers</li> <li>2. Accountability</li> </ol> </li> <li>• Documents that the study drugs/agents have been used according to the protocol.</li> <li>• Document the final accounting of study drugs/agents:             <ol style="list-style-type: none"> <li>1. Received at the site</li> <li>2. Dispensed to subjects</li> <li>3. Returned by subjects</li> <li>4. Returned to sponsor</li> </ol> </li> </ul>
Suggestions	<p>A sample accountability record is provided in the DAIDS Pharmacy Guidelines and Instructions. Site pharmacists are not required to use this exact form as long as the monitor can adequately determine the disposition of the agent.</p>
Reference	<ul style="list-style-type: none"> <li>• 21 CFR 312.62</li> <li>• FDA Guidance: E6 GCP, Sections 8.2.15, 8.3.8, 8.3.23, and 8.4.1</li> <li>• DAIDS SOP: Essential Documents</li> </ul>

### **Toxicities: grading (adverse events, signs and symptoms, lab results)**

Requirement	<ul style="list-style-type: none"> <li>• All toxicities and/or signs/symptoms, including those reported by the subject, must be recorded in the subject's research record and graded:             <ol style="list-style-type: none"> <li>1. An actual numerical grade that corresponds to the applicable toxicity table.</li> <li>2. A written description that corresponds to the definitions in the applicable toxicity table.</li> <li>3. Examples include:                 <ul style="list-style-type: none"> <li>➢ Chart Note</li> <li>➢ Flow sheet</li> <li>➢ Adverse Event (AE)/Symptom Checklist</li> <li>➢ Annotated lab slip, signed and dated by responsible clinician</li> <li>➢ Serious Adverse Event (SAE) form signed by clinician completing the form.</li> </ul> </li> <li>4. If toxicities and/or signs/symptoms are documented by non-study staff, the site staff must then document in the research record their assessment of the event, including grade and relationship to study drug/agent.</li> </ol> </li> </ul>
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Requirement Cont'd	<ul style="list-style-type: none"> <li>➤ For example, if a subject is seen in an emergency room for a stroke, the research clinician must document in the research record the grade and relationship of the event to the study drug/agent.</li> <li>• Reportable AEs/SAEs must have documentation to support the determination of relationship to study drug/agent when it is found to be "Not Related". (i.e., There must be an alternative, definitive etiology documented by the clinician.)</li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR312.62(b)</li> <li>• 21CFR312.64(b)</li> <li>• FDA Guidance: E6 GCP, Sections 2.3, 4.5.1, 4.11, 5.18.1, and 8.3.13</li> </ul>

### Transferring Subjects

Requirement	<ul style="list-style-type: none"> <li>• At a minimum, the transferring site will provide a written evaluation regarding the subject's condition along with a synopsis of the subject's involvement in the study. <ol style="list-style-type: none"> <li>1. Any supporting documentation deemed necessary is forwarded to the receiving site.</li> <li>2. If the receiving site requests additional subject records from the transferring site, document in the research record what is sent.</li> <li>3. Refer to your Group's own SOP regarding the transfer of subjects for additional requirements.</li> </ol> </li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• A transferring site, prior to the subject being evaluated by the receiving site, should send the relevant subject information/documentation.</li> <li>• It is the transferring site's responsibility to provide this information, and the receiving site's responsibility to review and request any additional information prior to the actual transfer.</li> </ul>
Reference	DAIDS Policy Group Policy

### Vital Signs and Other Assessments

Requirement	<ul style="list-style-type: none"> <li>• The protocol must specify the required vital signs (e.g., temperature, pulse, respirations, etc.) and other assessments (e.g., height, weight, body surface area, head circumference, etc.) and at which study visits they are required.</li> <li>• Record on one of the following: <ol style="list-style-type: none"> <li>1. Chart Note</li> <li>2. Flow sheet</li> <li>3. CRF used as source documentation</li> </ol> </li> </ul>
Suggestions	<p>Also refer to the following sections:</p> <ul style="list-style-type: none"> <li>• <u>Chart Note</u></li> <li>• <u>Case Report Forms</u></li> <li>• <u>Documentation Standards</u></li> <li>• <u>Flow sheets</u></li> <li>• <u>Initials</u></li> <li>• <u>Source Document</u></li> </ul>
Reference	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.5 and 6</li> </ul>

## **F.9. Essential Documents**

### **F.9.A. Purpose**

The purpose of this standard operating procedure (SOP) is to provide guidance to research personnel when a system of records is established. Essential documents are those documents that individually and collectively permit evaluation of both the conduct of a clinical trial and the quality of the data that are produced. These documents are generated throughout the various stages of a clinical trial, including, before the trial begins, during the conduct of the trial, and after completion or termination of the trial.

Essential documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of good clinical practice (GCP) and with all applicable regulatory requirements. These documents are also the ones that are usually audited by the sponsor and regulatory authorities as part of the process to confirm the validity of the trial conduct and integrity of the data.

### **F.9.B. Scope**

This SOP is based upon: 1) the Code of Federal Regulations (CFR), 2) guidances that apply to the involvement of human subjects in clinical research, and 3) standards for GCP. This SOP is applicable to all Division of AIDS (DAIDS) funded clinical trial sites conducting therapeutic, vaccine, or prevention studies on human subjects, both domestic and internationally.

### **F.9.C. Instructions**

- In addition to the list of essential documents in this SOP are, 1) a description of the purpose and/or requirements of each document, 2) a recommendation whether the document should be filed in a central file, protocol files, or subject records, and 3) a reference to the pertinent Federal regulation/guidance.
- It is acceptable to combine some of the documents, as long as the individual elements are readily identifiable. All documents do not have to be combined in one regulatory file.
- Regulatory files must be maintained for all trial sites. It is acceptable for a main site/center/unit to maintain regulatory files for their affiliated sites/subunits if necessary.
- A trial site is the location where the research is conducted and the term site is generally used in this document in place of the terms: unit, main unit, subunit, affiliated site, or center.
- All of the documents addressed in this SOP must be available for audit/inspection by the sponsor and regulatory authorities.
- Documents may be saved in an electronic format when appropriate.

- Always refer to local, state, institution, and/or institutional review board (IRB)/independent ethics committee (IEC) policies/regulations and follow any procedures that are more stringent than DAIDS SOPs.
- Informed consents and regulatory documents are not covered under the DAIDS policy for destroying case report forms (CRFs). Destruction or retention of these documents should be in accordance with Federal regulations and local institution/IRB/IEC policies and procedures.
- Resource tools (e.g., Lab Processing Charts) are not included as essential documents.

### F.9.D. Essential Documents SOP

Document	Requirement / Purpose	File	Reference
<b>Assent Form</b>	<p>Assent of children and permission of parents or legal guardians as determined by the IRB/IEC is required as per the provisions of 45CFR46.</p> <ul style="list-style-type: none"> <li>• State law where the research is taking place defines the age of a minor and requirements for emancipation.</li> <li>• Local IRB/IEC determine the age for obtaining assent.</li> <li>• The requirement for assent of children and/or permission of their parents or legal guardians may be waived by the IRB/IEC as long as the criteria for waiving consent in the regulations (45CFR46) are met.</li> <li>• Keep on file all versions submitted and approved by site's IRB/IEC.</li> </ul>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> <li>• Subject's research record</li> </ul>	<ul style="list-style-type: none"> <li>• 45CFR46, Subpart D</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• FDA Information Sheets, Guidance for IRBs and Investigators 1998 Update, FAQ Nos. 47 and 48; and Page 5</li> </ul>
<b>Assurance Number</b>	<p>The Institution is responsible for obtaining and maintaining a current Health &amp; Human Services (HHS) Assurance through the Office for Human Research Protections (OHRP).</p> <ul style="list-style-type: none"> <li>• The principal investigator (PI) is responsible for ensuring that a current Assurance is in effect while conducting research on human subjects in HHS funded studies.</li> <li>• All performance sites: <ul style="list-style-type: none"> <li>➢ Main site</li> <li>➢ All affiliated sites that meet the OHRP requirements for having an Assurance.</li> </ul> </li> <li>• Must be renewed prior to expiration.</li> <li>• Keep on file the Assurance number and expiration date.</li> </ul>	<ul style="list-style-type: none"> <li>• Central file</li> </ul> <p>Note: A copy of the actual Assurance document must be on file with the Institution and/or IRB/IEC.</p>	<ul style="list-style-type: none"> <li>• 45CFR46</li> <li>• OHRP Procedures for Registering IRBs and Filing Federalwide Assurances of Protection for Human Subjects (FWA)</li> </ul>
<b>Case Report Forms</b>	<ol style="list-style-type: none"> <li>1. Dated, completed case report forms (CRFs): <ul style="list-style-type: none"> <li>• To document that the investigator or authorized member of the investigator's staff confirms the observations recorded.</li> <li>• To document all changes/ additions or corrections made to CRF after initial data were recorded.</li> <li>• Signed if required by Group SOPs.</li> </ul> </li> <li>2. Originals retained by sponsor after study completion and/or site closure.</li> <li>3. Site retains copy. Refer to the DAIDS Source Documentation SOP for CRFs used as source documentation.</li> </ol>	<ul style="list-style-type: none"> <li>• Protocol file</li> <li>• Subject's research record</li> <li>• Data file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 Good Clinical Practice (GCP), Sections 1.11, 4.9, 5.5, 5.23, 8.3.14, 8.3.15</li> <li>• DAIDS SOP: Storage of CRFs and Pharmacy Records</li> <li>• DAIDS CRF Destruction List</li> <li>• DAIDS SOP: Source Documentation</li> </ul>
<b>Communications</b>	<ol style="list-style-type: none"> <li>1. All relevant communications, other than site visits, to document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, etc. For example: <ul style="list-style-type: none"> <li>• Letters</li> <li>• Meeting notes</li> <li>• Notes of telephone calls</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Sections 4.4, 4.9, 8.3.11</li> </ul>

<b>Communications Cont'd</b>	<ul style="list-style-type: none"> <li>• Email messages</li> </ul> <ol style="list-style-type: none"> <li>2. Includes communications to and from the Sponsor and/or the protocol team.</li> <li>3. Communications about a specific subject must be filed with source documents in the subject's research record.</li> <li>4. Save electronic media, originals, and/or certified copies.</li> </ol>		
<b>Curriculum Vitae (CV)</b>	<ol style="list-style-type: none"> <li>1. The site must have on file CVs and/or other relevant documents evidencing qualifications and eligibility to conduct the trial and/or provide medical supervision of subjects. Includes the following key personnel: <ul style="list-style-type: none"> <li>• Principal investigator (i.e., individual responsible for the grant/contract at the site).</li> <li>• Investigator responsible for day-to-day activities of the site.</li> <li>• For IND studies: <ul style="list-style-type: none"> <li>➢ Investigator of Record (IOR)</li> <li>➢ All other investigators/subinvestigators and any other clinicians listed on a Form FDA 1572, Box # 6.</li> </ul> </li> <li>• For non-IND studies, all other investigators/subinvestigators and any other clinicians listed on an authorized prescribers list.</li> </ul> </li> <li>• Study coordinator</li> <li>• Pharmacist of record</li> <ol style="list-style-type: none"> <li>2. Update to reflect significant changes: <ul style="list-style-type: none"> <li>• Affiliation</li> <li>• Education</li> <li>• Responsibilities</li> </ul> </li> <li>3. Refer to the DAIDS Protocol Registration Policy and Procedure Manual for additional requirements (e.g., CV content).</li> </ol> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.1, 4.3, 5.6, 8.2.10, 8.3.5</li> <li>• DAIDS Protocol Registration Policy and Procedure Manual</li> </ul>
<b>Final / Close-Out Monitoring Report</b>	<ol style="list-style-type: none"> <li>1. A close-out report by the monitor to document that all activities required for site close-out are completed and essential documents are in the appropriate files. Includes the following: <ul style="list-style-type: none"> <li>• Disposition of subjects</li> <li>• Location of research records</li> <li>• Disposition of specimens</li> <li>• Disposition of study drug</li> <li>• IRB/IEC notification</li> </ul> </li> <li>2. Applies only to sites being closed (i.e., no longer enrolling new subjects or following any subjects on-study).</li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.13, 8.4.5</li> </ul>
<b>Final Study Report</b>	<p>Final report by the investigator to the IRB/IEC, and where applicable, to the regulatory authorities to document completion of the trial. Include the following information:</p> <ul style="list-style-type: none"> <li>• Disposition of subjects</li> <li>• Location of research records</li> <li>• Disposition of specimens</li> <li>• Disposition of study drug</li> </ul> <p>Other information as required by the institution or local IRB/IEC (e.g., number of patients screened, number enrolled, serious adverse experiences, etc.).</p>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.13, 8.4.7</li> </ul>

<p><b>Financial Disclosure</b></p>	<ol style="list-style-type: none"> <li>1. To document financial aspects of the trial and the financial agreement between the investigator / institution and the sponsor for the trial.</li> <li>2. Certification or Disclosure <ul style="list-style-type: none"> <li>• Certify that there is no financial interest, or</li> <li>• Disclose specific financial interests.</li> <li>• Must complete Forms FDA 3454 or 3455, or equivalent forms.</li> </ul> </li> <li>3. Applies to investigators and subinvestigators</li> <li>4. Applies to individuals who fit any of the following criteria: <ul style="list-style-type: none"> <li>• Sign the Form FDA 1572 (Investigator of Record)</li> <li>• Identified as an investigator in initial submissions or protocol amendments under an IND.</li> <li>• Identified as an investigator in the NDA.</li> <li>• For studies not conducted under an IND, the individuals whom the sponsor considers to be investigators and subinvestigators.</li> <li>• Individuals who actually conduct and take responsibility for an investigation.</li> <li>• Individuals who have the ability and opportunity to significantly impact the data <i>as determined by the site</i>.</li> <li>• Spouses and dependent children of individuals indicated above.</li> </ul> </li> <li>5. Local institution, IRB/IEC and/or Group SOPs may have additional requirements.</li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR54</li> <li>• 42CFR50, Subpart F</li> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Section 8.2.4</li> <li>• FDA Guidance: Financial Disclosure by Clinical Investigators</li> <li>• NIH Notice OD-00-040</li> </ul>
<p><b>Form FDA 1572</b></p>	<ol style="list-style-type: none"> <li>1. Required for each initial protocol registration submission of a new protocol with an IND.</li> <li>2. The Investigator listed in box 1 of the 1572 is the individual who must sign and date the form. This individual is referred to as the Investigator of Record (IOR).</li> <li>3. Only laboratories not specified in the protocol need to be listed in Section 4.</li> <li>4. Section 6 must list any individual: <ul style="list-style-type: none"> <li>• Responsible for the medical management of subjects.</li> <li>• Authorized to prescribe study medication.</li> <li>• This may include, but is not limited to, the following: <ul style="list-style-type: none"> <li>➢ MDs</li> <li>➢ Pharmacists</li> <li>➢ Nurse Practitioner</li> <li>➢ Physician's Assistant</li> <li>➢ Study Coordinator</li> </ul> </li> <li>• If there are no individuals that need to be listed, then record "NONE".</li> </ul> </li> <li>5. Update as study personnel and/or other data on the form changes. Updated forms must be signed and dated by the IOR.</li> <li>6. The original version and any updated forms must be submitted to ROC for submission to the FDA.</li> <li>7. A copy of the forms must be kept on file at the site.</li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.1, 4.3</li> <li>• DAIDS Protocol Registration Policy and Procedure Manual</li> </ul>

<p><b>Information Given to Trial Subject</b></p>	<ol style="list-style-type: none"> <li>1. To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent.</li> <li>2. To document that recruitment measures are appropriate and not coercive.</li> <li>3. Include the following: <ul style="list-style-type: none"> <li>• Informed consent form</li> <li>• All applicable translations</li> <li>• Advertisement for subject recruitment (if used)</li> <li>• Education materials (protocol specific)</li> <li>• Any other written information</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 45CFR46</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• FDA Guidance: E6 GCP, Sections 4.8, 8.2.3</li> </ul>
<p><b>Informed Consent Form</b></p>	<ol style="list-style-type: none"> <li>1. Written informed consent form to document that consent is: <ul style="list-style-type: none"> <li>• Obtained in accordance with regulations, GCP, and protocol.</li> <li>• Dated prior to participation of each subject in trial.</li> <li>• Provided for direct access to records.</li> </ul> </li> <li>2. Non-English speaking subjects must be consented in a language they can understand. <ul style="list-style-type: none"> <li>• Save all written translations.</li> </ul> </li> <li>3. Consents obtained for screening purposes must be retained even if the subject was not enrolled in the protocol.</li> <li>4. To document revisions of these trial-related documents that take effect during trial, save all versions submitted and approved by site's IRB/IEC: <ul style="list-style-type: none"> <li>• Informed consent form.</li> <li>• Any other written information provided to subjects.</li> </ul> </li> <li>5. Continual reviews are at the directive of the site's IRB/IEC.</li> <li>6. Changes in consent forms due to protocol amendments and important safety information are at the directive of the site's IRB/IEC and/or DAIDS.</li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> <li>• Subject's research record</li> </ul>	<ul style="list-style-type: none"> <li>• 45CFR46</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.28, 4.8, 8.3.12, 8.2.3, 8.3.2</li> <li>• OHRP Informed Consent Guidance Information</li> </ul>
<p><b>Investigator's Brochures (IBs)</b></p>	<ol style="list-style-type: none"> <li>1. To document that relevant and current scientific information about the investigational drug/agent has been provided to the investigator.</li> <li>2. Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available.</li> <li>3. Keep on file a copy for EACH of the study drugs/agents used within the protocol.</li> <li>4. Include the following: <ul style="list-style-type: none"> <li>• Only the most recent version. <ul style="list-style-type: none"> <li>➢ All obsolete versions must be removed.</li> <li>➢ Obsolete IBs must be shredded since they may contain proprietary information.</li> <li>➢ Shred upon removal from file, or, upon trial completion.</li> </ul> </li> <li>• Addendum to IBs (e.g., all IND safety reports related to the drug/agent).</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.36, 5.12, 7, 8.2.1, 8.3.1</li> </ul>

<p style="text-align: center;"><b>IRB/IEC Approvals</b></p>	<ol style="list-style-type: none"> <li>1. Copies of all materials submitted to the IRB/IEC, including any local committees as required by the IRB/IEC, for example but not limited to: <ul style="list-style-type: none"> <li>• Clinical Research Center Committee</li> <li>• Radiation Safety Committee</li> <li>• Maternal Fetal Committee</li> <li>• Other Hospital Committees per local site IRB/IEC requirements</li> </ul> </li> <li>2. Dated proof of submission and IRB/IEC approval for the following for both initial submissions and submissions of revisions (if any). Revised documents must be labeled (e.g., date and/or version number) to differentiate them from previous versions. <ul style="list-style-type: none"> <li>• Advertisements – to document that recruitment measures are appropriate and not coercive.</li> <li>• Continuing/interim review of trial in accordance with regulations and local institution/IRB/IEC policy.</li> <li>• IND Safety Reports, Safety Memos, and Safety Alerts</li> <li>• Informed consent form</li> <li>• Investigator’s Brochures</li> <li>• Protocol</li> <li>• Protocol Amendments and/or Letters of Amendment</li> <li>• Protocol-specific education materials</li> <li>• Subject compensation</li> <li>• Any other documents receiving IRB/IEC approval or their favorable opinion.</li> <li>• Any other written information to be provided to subjects, to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent.</li> <li>• Any other pertinent communications with IRB/IEC or documentation required by the IRB/IEC.</li> <li>• Clarification memos <i>if required by local IRB/IEC</i>.</li> </ul> </li> <li>3. Proof of IRB/IEC receipt is necessary only if required by the local IRB/IEC.</li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 45CFR46</li> <li>• 21CFR50</li> <li>• 21CFR56</li> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 3, 4.4, 4.5, 4.10, 5.11, 5.17.3, 8.2.3, 8.2.7, 8.3.2, 8.3.3, 8.3.19</li> <li>• OHRP IRB Guidebook</li> </ul>
<p style="text-align: center;"><b>Laboratory</b></p>	<ol style="list-style-type: none"> <li>1. To document competence of local, central, or Group laboratories to perform protocol required tests and support reliability of results of medical/laboratory/standardized procedures/tests, one of the following must be on file: <ul style="list-style-type: none"> <li>• CLIA Certification of Compliance</li> <li>• CLIA Certification of Accreditation AND the agency certificate (e.g., CAP Certification of Accreditation)</li> <li>• Results of established quality control and/or external quality assessment (e.g., DAIDS VQA program)</li> <li>• Other validation</li> </ul> </li> <li>2. To document current competency, updated files when: <ul style="list-style-type: none"> <li>• Existing certification/accreditation/validation expires.</li> <li>• A new laboratory is added or replaces an existing laboratory.</li> </ul> </li> <li>3. Document normal values/ranges for medical/laboratory/standardized procedures/tests included in the protocol. <ul style="list-style-type: none"> <li>• Update when they are revised during the trial.</li> <li>• Does not apply to tests that do not have established normal values/ranges.</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Group-supported central laboratories documents may be filed on Group web sites.</li> <li>• Normal values/reference ranges may be filed in subject records (e.g., on lab report)</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR58</li> <li>• 21CFR312</li> <li>• 42CFR493.3</li> <li>• FDA Guidance: E6 GCP, Sections 4.2, 8.2.11, 8.2.12 8.3.6, 8.3.7</li> </ul>

<b>Laboratory Cont'd</b>	4. The preceding (1-3) do NOT apply to laboratories that test protocol specimens but do NOT report any subject-specific results for the diagnosis, treatment or assessment of the health of subjects.		
<b>Monitoring Log</b>	Dated signature of monitor for each study visit.	<ul style="list-style-type: none"> <li>• Central file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: Monitoring</li> <li>• FDA Guidance: E6 GCP, Section 5.18</li> </ul>
<b>Monitoring Reports</b>	Copies of all site visit reports (hard copy or electronic) to document both the site visits and findings of the monitor.	<ul style="list-style-type: none"> <li>• Central file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.39, 5.18, 8.3.10</li> </ul>
<b>Pharmacy Accountability Records</b>	Accountability records must be kept for all study drugs/agents provided as part of the protocol.	<ul style="list-style-type: none"> <li>• Pharmacy file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.6, 5.13, 5.14, 8.2.15, 8.3.8, 8.3.23, 8.4.1</li> </ul>
<b>Protocol</b>	<p>To document investigator and sponsor agreement to the protocol, amendments and CRFs; and, to document revisions of trial-related documents that take effect during trial:</p> <ul style="list-style-type: none"> <li>• Initial version that the site received registration approval for</li> <li>• Amendments and Letters of Amendment</li> <li>• Subsequent versions</li> <li>• Clarification memos</li> <li>• Case report forms</li> </ul>	<ul style="list-style-type: none"> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.44, 1.45, 4.5, 5.23, 6, 8.2.2, 8.3.2</li> </ul>
<b>Protocol Training</b>	<p>Documentation that trial procedures were reviewed with the investigator and investigator's trial staff:</p> <ul style="list-style-type: none"> <li>• Summary of start-up calls</li> <li>• Training meetings</li> </ul>	<ul style="list-style-type: none"> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.5, 5.23, 8.2.20</li> </ul>
<b>Record of Retained Body Fluids and/or Tissue Samples</b>	If any blood specimens, other body fluids and/or tissue samples are retained for long-term storage at the site/institution, document location and identification of the retained samples. (e.g., A laboratory data management or tracking system.)	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> <li>• Laboratory file</li> </ul>	<ul style="list-style-type: none"> <li>• FDA Guidance: E6 GCP, Section 8.3.25</li> <li>• OHRP Guidance: Issues to Consider in the Research Use of Stored Data or Tissues</li> </ul>

<p><b>Screening and Enrollment / Randomization Logs</b></p>	<ol style="list-style-type: none"> <li>To document identification of subjects who entered pretrial screening.</li> <li>To document chronological enrollment of subjects by trial number</li> <li>Screening and enrollment/randomization logs may be separate or combined.</li> <li>Include the following information: <ul style="list-style-type: none"> <li>Initials of all patients screened for each study</li> <li>PID if patient receives one</li> <li>Date screened</li> <li>Date randomized <ul style="list-style-type: none"> <li>➤ If not randomized, indicate reason</li> </ul> </li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>Central file</li> <li>Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>21CFR312</li> <li>FDA Guidance: E6 GCP, Sections 8.3.20, 8.3.22</li> </ul>
<p><b>Subject Identification Code List</b></p>	<ol style="list-style-type: none"> <li>To document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in the trial.</li> <li>Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required.</li> <li>List needs to be kept in a confidential manner.</li> </ol>	<ul style="list-style-type: none"> <li>Central file</li> <li>Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>FDA Guidance: E6 GCP, Sections 1.58, 8.3.21, 8.4.3</li> </ul>
<p><b>Serious Adverse Events (SAE) and Safety Reports</b></p>	<ol style="list-style-type: none"> <li>Notification by originating investigator to sponsor of serious adverse events, related reports, and other safety information.</li> <li>Notification by sponsor to investigators of safety information.</li> <li>Where applicable, notification by sponsor or investigator to regulatory authorities and IRB/IEC: <ul style="list-style-type: none"> <li>Unexpected serious adverse drug reactions</li> <li>Other safety information</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>Central file</li> <li>Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>45CFR46</li> <li>21CFR50</li> <li>21CFR56</li> <li>21CFR312</li> <li>FDA Guidance: E6 GCP, Sections 1.1, 1.2, 1.50, 1.60, 4.11, 5.16, 5.17, 8.3.16, 8.3.17, 8.3.18</li> <li>DAIDS SAE Reporting Manual</li> <li>DAIDS Policy for SAE Reporting on Non-IND Studies</li> </ul>
<p><b>Signature Key/Log</b></p>	<ol style="list-style-type: none"> <li>To document the signatures of individuals using initials in place of a full signature to sign CRFs and source documents.</li> <li>To document the signatures and initials of all persons authorized to make entries and/or corrections on CRFs. Include all site staff working on a study, such as: <ul style="list-style-type: none"> <li>Clinicians</li> <li>Physicians</li> <li>Pharmacists</li> <li>Data personnel</li> <li>Any other individuals authorized to make entries and/or corrections on CRFs.</li> </ul> </li> <li>Key/log must include: <ul style="list-style-type: none"> <li>Initials</li> <li>Printed Signature</li> <li>Legal Signature, including first and last name Credentials (if appropriate)</li> </ul> </li> </ol>	<ul style="list-style-type: none"> <li>Central file</li> <li>Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>FDA Guidance: E6 GCP, Section 8.3.24</li> </ul>

<p><b>Signed Agreements</b></p>	<p>To document agreements between involved parties, if any. For example:</p> <ul style="list-style-type: none"> <li>• Investigator/institution and sponsor (e.g., grant)</li> <li>• Investigator/institution and affiliated sites (e.g., contracts)</li> <li>• Investigator/institution and authorities (where required)</li> </ul>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Business office file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 4.9.6, 5.6, 8.2.6</li> </ul>
<p><b>Source Documents</b></p>	<ol style="list-style-type: none"> <li>1. To document the existence of the subject and substantiate integrity of trial data collected.</li> <li>2. To include original documents related to the trial, medical treatment, and history of subject.</li> <li>3. Electronic media, original documents or certified copies.</li> <li>4. Refer to the DAIDS Source Documentation SOP for additional requirements.</li> </ol>	<ul style="list-style-type: none"> <li>• As per requirements of local institution.</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR11</li> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.51, 1.52, 5.20, 8.3.13</li> </ul>
<p><b>Unblinding</b></p>	<p>A copy of the Group's SOP for unblinding must be on file at the site.</p>	<ul style="list-style-type: none"> <li>• Central file</li> <li>• Protocol file</li> </ul>	<ul style="list-style-type: none"> <li>• 21CFR312</li> <li>• FDA Guidance: E6 GCP, Sections 1.10, 4.7, 8.2.17, 8.4.6</li> </ul>

## G. SITE MONITORING

### Clinical Site/Center Monitoring

#### G.1. Purpose

Since the Division of AIDS (DAIDS) currently holds the Investigational New Drug (IND) Application for many of the clinical trials funded by the Therapeutics Research Program (TRP), it is our policy, as sponsor, to fully comply with obligations to monitor trials under 21 Code of Federal Regulations (CFR) 312.

The Food and Drug Administration (FDA)/International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) Guidelines Section 5.18.1. defines the purpose of monitoring clinical trials as follows:

- To verify that the rights and well-being of human subjects are protected;
- To verify that the reported trial data are accurate, complete and verifiable from the source documents; and
- To verify that the conduct of the trial is in compliance with the currently approved protocol/amendment (s), with GCP, and with the applicable regulatory requirements.

To accomplish this task, DAIDS has delegated clinical site monitoring responsibility to a Contract Research Organization (CRO) known as the Clinical Site Monitoring Group (CSMG). The CSMG will perform periodic on-site visits to sites conducting DAIDS-sponsored clinical trials and report findings to DAIDS.

Monitoring visits may be of several types including: Initiation Visits, Interim Visits, Site Closeout Visits, and Special Assignment Visits. It is anticipated that approximately 50 percent of the monitor's time on site will be directed toward an assessment of those areas of the trials that most directly affect subject safety. These include, but are not limited to, a review of: the informed consent documents and eligibility criteria, the dispensing and accountability of investigational study products, correct implementation of the protocol, internal site quality control and quality assurance procedures, adherence to Good Clinical Practice Guidelines, and a review of regulatory documentation. The additional 50 percent of the time should be devoted to an examination of source documents to assess their accuracy and completeness. This review of the data could be a verification of source documents (SD) to case report forms (CRFs) or a review of the database back to source documents. Where possible this **general guidance** will be followed; however, special assignments or other competing priorities may take precedence.

## **G.2. Development of Monitoring Assignments**

Typically, monitoring assignments are developed quarterly. The CRMB Program Coordinators, the CSMG contractor, the Regulatory Affairs Branch (RAB), and the Pharmaceutical Affairs Branch (PAB) share the responsibility for generation of the assignments. Others that provide requests for the assignments may include the data management centers, protocol teams, or the associated Executive/Steering/Evaluation committees of the specific groups.

## **G.3. Interim Monitoring Visit**

The typical Interim Site Monitoring Visit may include the following:

- An evaluation of the overall status of the site/center in relation to the specific assignment
- A discussion of pending issues and outstanding actions from a previous visit
- A review of protocol compliance
- A review of the Informed Consents
- A review of the status of the Investigational Product (IP)
- A review of Regulatory Compliance
- A review of the Source Documentation
- A discussion of corrective actions and administrative issues
- A debriefing for the Investigator and designated staff
- A complete documentation of all visit findings

## **G.4. Site Visit Report (SVR)**

Each monitoring visit is fully documented in the Site Visit Report (SVR). As noted in the GCP Guidelines (5.18.4 n and q), the monitors are obligated to inform the Investigator of any Case Report Form entry, error, omission, or illegibility discovered. Additionally, the monitor must communicate any deviations from the protocol, SOPs, GCP, or regulatory requirements. As sponsor, DAIDS is required to take prompt action to secure compliance when there has been a report of noncompliance.

Actions taken following issue of final SVR:

- SVR is distributed to DAIDS staff, the Investigator of the site/center, the appropriate data management center, and possibly the Regulatory Operations Center.
- DAIDS Program Coordinators review SVRs.
- If there are no significant findings the report is filed.
- If significant findings are identified, the Program Coordinator will contact the site/center and CSMG for clarification.
- The Program Coordinators will document/ follow-up on outstanding issues and will work with the sites/centers to ensure future compliance.

## **G.5. Resolution of Differences**

The determination and reporting of protocol violations and deviations serve two distinct purposes in DAIDS-funded trials:

1. The results of clinical site monitoring, as noted in the SVR, are **primarily** used by DAIDS as a tool for monitoring the performance of clinical trials in fulfillment of our obligations as sponsor under 21 CFR 312. As a matter of policy, research records are reviewed to determine if the protocol **as written** is being followed.
2. Additionally, the results of clinical site monitoring are also used by the cooperative groups to measure individual site performance against the performance of the Group.

Therefore, when differences in interpretation of the protocol requirements are encountered, the following procedure for a resolution will be followed:

- Both Principal Investigator (PI) and CSMG will notify CRMB Program Coordinator.
- CRMB Program Coordinator will consult with the protocol team.
- CRMB Program Coordinator will make the final decision about whether or not a protocol violation will be assigned.
- If necessary, a revised SVR will be issued.
- CRMB Program Coordinator will notify the PI and CSMG of the decision and rationale.

In terms of the overall performance evaluation as reported to the Group leadership, the PI may appeal the decision to the appropriate committee. The Group leadership may determine that the protocol violation should receive “special consideration” in their evaluation of the site’s performance. It should be noted, however, that this “special consideration” of a protocol violation does not alter the decision of the CRMB Program Coordinator.

## **H. WORKING INSTRUCTIONS FOR SITE/CENTER OPERATIONS**

### **H.1. Office for Human Research Protection (OHRP) Assurance of Compliance**

#### **What is an Assurance of Compliance?**

An Assurance is a document approved by OHRP from a prospective awardee or other institutional performance site that will engage in Department of Health and Human Services (DHHS) conducted or supported research. It assures institutional compliance with and implementation of regulations for the protection of human subjects (45 CFR 46).

All Assurance documents include text, an IRB membership list, and a signature page. An institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. See OHRP Letter dated January 26, 1999, titled Engagement of Institutions in Research under Assurance Documents, OHRP Web page. An Assurance must be in place before funds are released.

For further assurance information and sample documents see the OHRP Web page at:  
<http://ohrp.osophs.dhhs.gov/>

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## H.2. Division of AIDS (DAIDS) Site Establishment Form

1. Name of the Site/Center being established.  
Address
2. Is the site that is being established a new clinical site or an affiliated site/center of a site/center that is already established?
3. If site/center is an affiliated site, what is the name of the sponsoring site/center?  
Site Name  
Address
4. What is the Health and Human Services Assurance Number assigned to this site/center to conduct clinical research that involves human subjects?  
  
Assurance Number \_\_\_\_\_ Expiration Date \_\_\_\_\_
5. Will prisoners be enrolled or followed?
6. Institutional Review Board responsible for this site.  
Name  
Address
7. Principal Investigator (PI).  
Name and title  
Address  
Telephone, FAX number, and Internet address
8. Investigator at this site who is responsible for the day-to-day clinical and administrative activities. A copy of the CV for the investigator is to be included with this form.  
Name and title  
Address  
Telephone, FAX number, and Internet address
9. Study coordinator at this site. A copy of the CV for the study coordinator is to be included with this form.  
Name and Title  
Address  
Telephone, FAX number, and Internet address
10. Data manager at this site.  
Name and title  
Address  
Telephone, FAX number, and Internet address

11. Name of staff member to whom all data reports (e.g., delinquency reports, unanswered queries, unresolved error reports) should be sent from the data.

Management Center (DMC)

Name

Address

Telephone, FAX number, and Internet address

**NOTE:** If this form is for an affiliated site/center, should data reports from the DMC go to the sponsoring clinical site designee only or both the sponsoring clinical site designee and the affiliated site/center designee?

This form is to be updated when information changes and submitted electronically to the DAIDS Program Coordinator.

### **H.3. Pharmacy Establishment**

**NOTE: This Pharmacy Plan must be completed by the Pharmacist of Record.**

As a sponsor of Investigational New Drug (IND) applications, the DAIDS of the National Institute of Allergy and Infectious Disease (NIAID) must comply with the Food and Drug Administration (FDA) Code of Federal Regulations (CFR) governing the receipt, use, and disposition of investigational agents. The DAIDS has the responsibility to assure that all investigators establish and maintain adequate records of agent receipt, use, and disposition that comply with FDA regulations and the standards of research involving the use of investigational agents.

The pharmacist at each DAIDS-sponsored site, designated as the Pharmacist of Record, is the primary individual who is expected to develop and maintain an investigational agent control system, which includes the technical procedures for agent ordering, control, dispensing, and accountability. In addition, the Pharmacist of Record is responsible for the establishment of internal policies and procedures for the safe and proper use of investigational agents. The Pharmacist of Record will perform the day-to-day dispensing and accountability activities.

A pharmacy plan shall be created by the Pharmacist of Record for each clinical research site participating in DAIDS-sponsored studies, addressing the control and use of Investigational Agents. The pharmacy plan for a clinical research site must be submitted to the DAIDS Pharmaceutical Affairs Branch for approval prior to the receipt and distribution of study medication. The Pharmacist of Record is encouraged to work with other staff members on the formulation of this plan.

- If a Pharmacist of Record will be responsible for dispensing activities at more than one clinical site, provide a separate pharmacy plan for each clinical research site.
- In the event that a Site Pharmacist is responsible for the dispensing of investigational agents to subjects enrolled on protocols at other sites (hospitals and clinics), a letter describing the dispensing procedures must be co-signed by the IRB Chairman and the Director of Pharmacy at the second site. This letter serves to document the concurrence of these individuals with the proposed plan for dispensing of investigational agents to subjects at that site. This letter also serves to notify the DAIDS that all parties have been properly notified of these procedures.

The DAIDS Pharmaceutical Affairs Branch shall be informed of any procedural changes in the handling of the investigational agents, as they occur.

If there is a change in the Pharmacist of Record after the DAIDS Pharmacy Establishment Plan is approved, complete and submit the form found on page 6 of this document.

If you have any questions, contact Ana I. Martinez, R.Ph., Chief, Pharmaceutical Affairs Branch or other branch staff at 011-301-496-8213.

### **H.3.A. Background**

1. Name, address, and site number of the clinical research site this pharmacy plan is for.
2. Name, degree, title or position, site mailing address, Internet address (if any), telephone, and fax numbers of the Pharmacist of Record who is responsible for this pharmacy plan  
*Note: All pharmacy-related correspondence will be sent to the contact information provided below.*
3. Shipping address where study products are to be shipped.
4. Name, degree, title or position of the back-up Pharmacist who will assume these responsibilities when the Pharmacist of Record is not available.
5. Does the pharmacy have written policies and procedures for handling investigational agents? If yes, attach.
6. Describe the system for organizing protocol information (for example, the current IRB-approved version of the protocol [and amendments if applicable], subject treatment assignment lists, order forms, packing slips, accountability records, written prescriptions, return records, letters and memos from DAIDS, Investigator's Brochures, etc.), the process for keeping this information up to date, where it will be located, and who will have access.
7. How will the Pharmacist of Record be informed of the IRB approval of a protocol? How will the Pharmacist of Record verify that s/he is working with the current IRB-approved version of a protocol?
8. How will authorized prescribers be identified for a protocol so as to prevent the unauthorized prescribing of investigational agents?
9. What procedures will be followed by the Pharmacist of Record to maintain confidentiality of a subject's pharmacy file and the investigational agent accountability records?

10. Does the pharmacy utilize a computerized investigational drug system (e.g., accountability/inventory, study information and/or medication order entry)? If so, describe.

11. Will the Pharmacist of Record be involved in subject consultation/counseling?

### **H.3.B. Investigational Agent Control**

Each of the following questions must be answered.

#### 1. Room Temperature Storage

- a. Where will investigational agents be stored?
- b. Who will have access to investigational agents?
- c. How will access to investigational agents be limited to only those listed in b) above?
- d. If prescriptions are prepared prior to a subject's visit, where will they be stored?
- e. Is the access limited in this storage area?

#### 2. Refrigerated Storage in the Pharmacy

- a. Is refrigeration available?
- b. Where is the refrigerator located?
- c. How large is the refrigerator? Indicate whether cubic feet or cubic meters.
- d. Who will have access to the refrigerator?
- e. How will access to the refrigerator be limited?
- f. At what temperature is the refrigerator maintained?
- g. How often is the refrigerator monitored for temperature control?
- h. Is there documentation of the temperature monitoring of the refrigerator?

#### 3. Refrigerated Storage in the Clinic

- a. If study agents that require refrigeration are prepared in advance for a subject's collection (pick up) at the clinic, will refrigeration be available in the clinic?
- b. How is access to the refrigerator in this area limited?

#### 4. Freezer Storage in the Pharmacy

- a. Is a  $-20$  to  $-10^{\circ}$  C ( $-4$  to  $14^{\circ}$ F) freezer available?
- b. If yes, where is the freezer located?
- c. How large is the freezer? Indicate whether cubic feet or cubic meters.
- d. Who will have access to the freezer?
- e. How will access to the freezer be limited?
- f. At what temperature is the freezer maintained?
- g. How often is the freezer monitored for temperature control?
- h. Is there documentation of the temperature monitoring of the freezer?

#### 5. Minus $70^{\circ}$ C Freezer Storage Space Availability

- a. Is  $-70^{\circ}$ C freezer storage space available?
- b. If yes, where is this  $-70^{\circ}$ C freezer storage space located?
- c. How many cubic feet or cubic meters are available?
- d. Who will have access to the  $-70^{\circ}$ C freezer storage space?
- e. How will access to the  $-70^{\circ}$ C freezer storage space be limited?
- f. At what temperature is the  $-70^{\circ}$ C freezer storage space maintained?
- g. How often is the  $-70^{\circ}$ C freezer monitored for temperature control?
- h. Is there documentation of the temperature monitoring of the  $-70^{\circ}$  C freezer?

6. How often will the investigational agents/study drugs on the shelves and in the refrigerator/freezer be counted and compared with the accountability record? The Pharmacist of Record is required to keep complete written records (accountability records) of all investigational agents/study drugs that are received from the NIAID Clinical Research Products Management Center and of all investigational agents/study drugs that are dispensed to subjects. The count or quantity of investigational agents/study drugs that you have at your site must match the quantity on the accountability records at all times.

### H.3.C. Investigational Agent Dispensing

1. An authorized prescriber listed on the FDA form 1572 must sign a written prescription at the time that a subject is registered/randomized to the protocol or when there is a change in treatment, in order for the pharmacist to dispense medications. How will the Pharmacist of Record receive this written prescription? (If electronic prescriptions are used describe this process.)
2. Describe how an initial written study medication order will be prepared and dispensed at this institution. Will these medications be prepared in the inpatient or outpatient pharmacy? (If both, describe both procedures.)
3. How will it be documented that the informed consent was signed prior to dispensing the investigational agent(s)?
4. How will the Pharmacist of Record be informed that subsequent prescriptions/refills need to be prepared? How will study agents be delivered to the subject for follow-up visits?
5. Written prescriptions must be used to notify the Pharmacist of Record when a study drug dose is changed. How will the Pharmacist of Record receive the written prescription that notifies that a dose has been changed?
6. Is a biological safety cabinet or an isolator available for preparing subjects' medications that need to be sterile?
7. How will the Pharmacist of Record dispense study agents? (check all that apply)  
 Directly to subjects.  
 Deliver study agents to other healthcare providers who will distribute it to subjects.  
 Through other procedures (describe).
8. How will the Pharmacist of Record receive study drugs returned by the subject? (check all that apply)  
 Directly from subjects.  
 From other healthcare providers.  
 Through other procedures (describe).

Pharmacist of Record Signature \_\_\_\_\_ Date \_\_\_\_\_

**NOTE: Pharmacy plans will not be approved without the Pharmacist of Record's dated signature and an attached copy of the Pharmacist of Record's curriculum vitae. A copy of this completed DAIDS Pharmacy Establishment Plan must be kept on file in the pharmacy.**

**I have on file a copy of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Group dated \_\_\_\_\_ which I have reviewed.**

Signature \_\_\_\_\_ Date \_\_\_\_\_

**H.3.D. Temporary / Permanent Notification of Change in Pharmacist of Record**

This letter serves to notify the Pharmaceutical Affairs Branch at the Division of AIDS of a change in the Pharmacist of Record:

Permanent: \_\_\_\_\_

Temporary: \_\_\_\_\_ Date From: \_\_\_\_\_ Date To: \_\_\_\_\_

Site Name: \_\_\_\_\_ Site Number (s): \_\_\_\_\_

Name of PREVIOUS Pharmacist of Record: \_\_\_\_\_

**The following information may be provided as an attachment, (see CV requirement below)**

Name of NEW Pharmacist of Record: \_\_\_\_\_

Degree, Title, Position: \_\_\_\_\_

Mailing address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone number: \_\_\_\_\_

Fax number: \_\_\_\_\_

Internet address (if any): \_\_\_\_\_

**Please complete the following:**

\_\_\_\_\_(Initial here) I agree to comply with all of the information contained in the previous or revised Division of AIDS Pharmacy Establishment Plan. **If the pharmacy plan was revised, please attach.**

I have on file a copy of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Group, **with the print date:** \_\_\_\_\_ which I have reviewed.

**Sign and date:**

\_\_\_\_\_  
**Signature** of NEW Pharmacist of Record

\_\_\_\_\_  
**Date**

**Send:**

- 1) This completed form, **signed and dated**
- 2) A copy of the **C.V.** for the New Pharmacist of Record
- 3) The **Revised** Division of AIDS Pharmacy Establishment Plan (**if applicable**) to:

**Ana I. Martinez, R.Ph.**  
**Chief, Pharmaceutical Affairs Branch**  
**NIH/NIAID/DAIDS Room 5115**  
**6700 B Rockledge Drive, MSC 7620**  
**Bethesda, MD 20892-7620 USA**  
**Phone: (301) 496-8213 Fax: (301) 402-1506**

#### H.4. Quality Management Plan Annual Evaluation

Site Name: \_\_\_\_\_ Site Number: \_\_\_\_\_

**The Division of AIDS requires site personnel to evaluate Quality Management (QM) Plans annually. Please complete this form and submit it electronically to the Clinical Research Management Branch (CRMB) Program Coordinator.**

##### Quality Assurance (QA)

1. How many research records (source documents that have been compared to case report forms) have been audited during the past year for QA? Indicate the number for the main clinical site and each subsite separately.
2. Which of the following key indicators are audited in your QA process?

Informed Consents	Missed Visit documentation and follow-up	Eligibility Criteria
Regulatory Audits	Laboratory Results	Concomitant Medications
Drug Dosing	Adverse Events/Serious Adverse Events	Clinical Endpoints
Other (Specify)		
3. Which key indicators revealed a need for improvement?

##### Quality Control (QC)

4. What QC tools are included in your QM Plan?
5. Which tools revealed a need for improvement?
6. What percentage of case report forms are reviewed for QC prior to keying?

##### QM Plan Evaluation Summary

7. Has your QM plan been successful in identifying QA or QC areas in need of improvement? Yes \_\_\_\_\_ No \_\_\_\_\_  
If yes, what plans have you implemented for improvement?
8. Will you change anything in your plan for the upcoming year?  
Yes \_\_\_\_\_ No \_\_\_\_\_ If yes, what will you change?
9. How and how often were QM results communicated to staff?
10. What was done to educate and train new staff?
11. What was done to provide continuing education? How often?
12. How is it ensured that staff are appropriately qualified and trained?

13. How often did QM meetings take place where minutes were recorded?

14. Other Comments:

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Signature of Study Coordinator or Principal Investigator

Date

## **H.5. Budget/Grants Management**

### **H.5.A. GLOSSARY OF NIH GRANT TERMS**

The information provided in this section is an overview of grants policy and CRMB procedures. For more detailed grants information, go to the NIH Office of Extramural Research Web page: <http://grants.nih.gov/grants/oeer.htm>.

**Budget Period:** The interval of time (usually 12 months) into which a project period is divided for budgetary and funding purposes.

**Competing Continuation Application (Type 2):** A request for funding to renew, by one or more additional budget periods, a project period that would otherwise expire.

**Consortium Agreement:** A collaborative arrangement in support of a research project in which some portion of the programmatic activity is carried out through a formalized agreement between the grantee and one or more other organizations that are separate legal entities administratively independent of the grantee.

**Contract Under a Grant:** A written agreement between a grantee and a third party to acquire routine goods or services.

**Cooperative Agreement (U01):** A financial assistance mechanism used when substantial Federal programmatic involvement with the recipient during performance is anticipated by the NIH Institute or Center.

**Direct Costs:** Costs that can be specifically identified with a particular project(s) or activity.

**Facilities and Administrative Costs:** Costs that are incurred by a grantee for common or joint objectives and that, therefore, cannot be identified specifically with a particular project or program. These costs were previously known as "indirect costs," and, in most instances, will be referred to in this document as "F&A costs."

**Financial Status Report (FSR):** A report of expenditures required as documentation of the financial status of grants according to the official accounting records of the grantee organization. The report must be submitted for each budget period no later than 90 days after the close of the budget period.

**Grant:** A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity. A grant is used whenever the NIH awarding office anticipates no substantial programmatic involvement with the recipient during performance of the financially assisted activities.

**Grants Management Officer (GMO):** An NIH official responsible for the business management aspects of grants and cooperative agreements, including review, negotiation, award, and administration, and for the interpretation of grants administration policies and provisions.

Only GMOs are authorized to obligate NIH to the expenditure of funds and to make changes to approved projects on behalf of NIH. Each NIH Institute and Center that awards grants has one or more GMOs with responsibility for particular programs or awards.

**Indirect Costs:** Refer to definition of "Facilities and Administrative."

**Key Personnel:** Those individuals noted in the administrative terms included in the NGA.

**New Application (Type 1):** A request for financial assistance for a project or activity that is not currently receiving NIH support and must compete for support.

**Non-competing Continuation Application (Type 5):** A request for funding for the second or subsequent budget period within an approved project period.

**Notice of Grant Award (NGA):** The legally binding document that notifies the grantee and others that an award has been made, contains or references all terms and conditions of the award, and documents the obligation of Federal funds. The award notice may be in letter format and may be issued electronically.

**Project Period:** The total time for which support of a project has been programmatically approved. The total project period is comprised of the initial competitive segment, any subsequent competitive segment(s) resulting from a competing continuation award(s), and any non-competing extensions.

**Program Official:** The NIH Institute or Center official responsible for the programmatic, scientific, and/or technical aspects of a grant.

**Rebudget:** To transfer funds from one budget category to another, e.g., to move funds from the budget category "equipment" to the budget category "personnel."

**Restricted Funds:** Portions of an award may be restricted either for use for a specific purpose only or are restricted pending the receipt of information or documentation.

**Terms and Conditions of Award:** All legal requirements imposed on a grant by NIH, whether based on statute, regulation, policy, or other document referenced in the grant award, or specified by the grant award document itself. The Notice of Grant Award may include both standard and special conditions that are considered necessary to attain the grant's objectives, facilitate postaward administration of the grant, conserve grant funds, or otherwise protect the Federal Government's interests.

**Total Project Costs:** The total allowable costs (both direct costs and facilities and administrative costs) incurred by the grantee to carry out a grant-supported project or activity. Total project costs include costs charged to the NIH grant and costs borne by the grantee to satisfy a matching or cost-sharing requirement.

**Unobligated Balance:** Unexpended funds at the end of a given budget period.

**Withheld Funds:** A portion of a grant award may not be awarded at the beginning of a budget period for various reasons such as poor performance or lack of required information. Funds may be awarded later in the budget period, if the problem is resolved.

**U01:** A U01 Award is a Research Project Cooperative Agreement. This award is used to support a discrete, specified, circumscribed project to be performed by named investigators in an area representing specific interest and competencies.

## **H.6. Storage of Case Report Forms and Pharmacy Records**

### **PURPOSE**

This standard operating procedure (SOP) describes the procedures for storage of case report forms (CRFs) and pharmacy records for the Division of AIDS (DAIDS) sponsored clinical trials at DAIDS/TRP-sponsored sites that close. This procedure should be utilized at the end of the site's phase-out period.

### **POINT OF CONTACT**

DAIDS, Regulatory Affairs Branch (RAB) is responsible for the management of this SOP. The Regulatory Operations Center (ROC) is responsible for receiving and re-packing CRFs and pharmacy records for storage at the Washington National Records Center (WNRC). The Records Coordinator at ROC is the contact person, and may be reached at (301) 770-4550.

### **OBJECTIVES**

As sponsor, DAIDS/TRP provides storage for CRFs and pharmacy records at WNRC for DAIDS/TRP-sponsored clinical sites that close. These records must be organized and stored by protocol and subject should there be a need for future retrieval.

### **SCOPE**

Only CRFs and pharmacy records from DAIDS/TRP-sponsored clinical trials will be stored at the WNRC. DAIDS/TRP will only provide this service to clinical sites that close.

### **RESPONSIBILITY**

The Principal Investigator (PI) is responsible for appropriately managing the storage of research and regulatory records when a site/center closes.

## **H.6.A. PROCEDURES**

Identifying records for storage:

- What to send:
  1. Case report forms
  2. Pharmacy records
  
- What not to send:
  1. Signed informed consents
  2. Copies of protocol
  3. Site registration records
  4. Regulatory documents (Examples of regulatory documents include but may not be limited to Institutional Review Board/Ethics Committee approvals for protocols, amendments and informed consents; official notices from the DAIDS, Protocol Team, Site Registration Office, data managers and monitors; and documentation from the PI to any of the above. Also, all pertinent research correspondence [e.g., e-mail messages, faxes, and letters]).

**NOTE:** Study documents (1 through 4), as noted above, must be maintained at the site for three years after the site/center has closed.

5. The original research records, clinic notes, and hospital notes are kept on site and preserved according to institutional policy.

#### **H.6.B. Packing CRFs and Pharmacy Records for Storage by DAIDS/ROC:**

1. Use strong packing boxes that will not break during shipping.
2. Remove each subject's CRFs from the notebook binder and place intact in manila folders or bind them in such a way that the forms do not tear or become dislodged during shipping.
3. Keep the Subject Identification (PIDs) in numerical order when packing the CRFs of each protocol.
4. Pack pharmacy accountability records in a separate folder or envelope. The pharmacy records should be bound separately, well identified and included either at the front of the first box or the back of the last box. The study coordinator should work with the site pharmacist to determine how and when the packing should take place.
5. Send all CRFs for a protocol in one shipment. It is important not to split the CRFs of one protocol between two separate shipments. It is acceptable to send several protocols in one shipment.
6. Include the following information IN EACH BOX:
  - a. Name and number of the site/center or affiliated site/center;
  - b. Name of the PI;
  - c. Protocol number(s) that are packed in that box;
  - d. Complete list of PIDS, by protocol, in numerical order; and
  - e. A copy of the master list (see number 7 below).
7. Send the same information printed on a master list (composite list of all information in all of the boxes of each shipment) to the Records Coordinator at ROC, and retain a copy for the PI's files (to be kept for a period of three years). Also include the master list inside each box. Box lists and master lists are important in case the shipment is partially or completely lost.
8. Contact the Records Coordinator at ROC to receive permission to send the boxes to ROC.
9. Dispatch the shipment so that ROC will receive the boxes on a workday (never on a weekend or holiday).

#### **H.6.C. Shipping CRFs and Pharmacy Records**

1. The site is responsible for shipping costs.
2. Number each box in the following manner:
  - a. The number of the particular box and the total number of boxes sent in that mailing. For example: 5 of 8. This indicates box number 5 in a shipment of 8 boxes.
  - b. The placement of this number, 5 of 8, should be on the ends or sides of the box, not the top or bottom

3. Send the boxes by UPS, Parcel Post, Federal Express, or other carrier to:

Records Coordinator.  
Regulatory Operations Office  
6101 Executive Blvd., Suite 200  
Rockville, MD 20853  
(301) 770-4550

4. Notify the Records Coordinator at ROC of the expected arrival date of the boxes and the number of boxes that have been sent.
5. The Records Coordinator will send a message back to the site/center when the boxes arrive at the ROC.

## **H.7. Abbreviations and Acronyms**

### **NIH and Related Research Organizations**

AACTG	Adult AIDS Clinical Trials Group
ACTIS	AIDS Clinical Trials Information Service
ARAC	AIDS Research Advisory Committee
ATIS	AIDS Treatment Information Service
BSP	Basic Sciences Program
CDC	Centers for Disease Control and Prevention
CPCRA	The Terry Bein Community Programs for Clinical Research on AIDS
CRMB	Clinical Research Management Branch
CSMG	Clinical Site Monitoring Group
CSRC	Clinical Science Review Committee
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FIC	Fogarty International Center
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
MACS	Multicenter AIDS Cohort Studies
MSG	Mycoses Study Group
NAAIDC	National Advisory Allergy and Infectious Disease Council
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OAR	Office of AIDS Research
OHRP	Office for Human Research Protections
PACTG	Pediatric AIDS Clinical Trials Group
PHS	Public Health Service
PAB	Pharmaceutical Affairs Branch
RAB	Regulatory Affairs Branch
ROC	Regulatory Operations Center
SOCA	Studies of the Ocular Complications of AIDS
TRP	Therapeutics Research Program
VPRP	Vaccine and Prevention Research Program
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study

### **Other Acronyms**

AE	Adverse Event/Experience
AER	Adverse Experience Report
AIDS	Acquired Immunodeficiency Syndrome
CAB	Community Advisory Board

CCG	Community Constituency Group
CFR	Code of Federal Regulations
CRF	Case Report Form
CS	Concept Sheet
CTA	Clinical Trials Agreement
CTAAG	Clinical Trials At A Glance Report
CTS	Clinical Trials Specialist
EC	Ethics Committee
FY	Fiscal Year
GCP	Good Clinical Practice
GCRC	General Clinical Research Center
GLP	Good Laboratory Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IoR	Investigator of Record
IRB	Institutional Review Board
LFU	Lost to Follow-up
LOU	Letter of Understanding
MM	Medical Monitor
MO	Medical Officer
MOOP	Manual of Operations
MOU	Memorandum of Understanding
NCAB	National Community Advisory Board
NDA	New Drug Application
NWCS	New Work Concept Sheet
PC	Project Coordinator
PI	Principal Investigator
PID	Patient/Subject Identification Number
PLWA	Person Living With AIDS
PSR	Protocol Status Report
PWA	Person With AIDS
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
QoL	Quality of Life
RFA	Request for Applications
RFP	Request for Proposals
SAE	Serious Adverse Event/Experience
SID	Study Identification Number
SOP	Standard Operation Procedure

## H.8. Glossary of Research Terms

**Affiliated Site/Center:** A site/center that is sponsored by another site/center that is already a member of a clinical trials group.

**Clinical Research Site/Center:** A place where subjects are evaluated and treated according to a research protocol.

**Coordinating Center:** A central unit responsible for receipt and distribution of information and/or clinical trials materials.

**Data Manager:** The person responsible for the management of clinical data. This includes, but is not limited to: 1) collecting, maintaining, and monitoring clinical trial data, 2) organizing and preparing weekly study forms, study spreadsheets, laboratory requisitions, and other materials required by the protocols, 3) implementing quality measures including the regular review of study and medical records, 4) evaluating and ensuring the accuracy and completeness of subject data, 5) assisting the data monitoring staff at the Data Management Center in verifying, correcting, or obtaining data, and 6) transferring data to the Data Management Center/Statistical Center.

**Investigator of Record:** The physician designated by the PI who is responsible for ensuring that a specific clinical investigation is conducted according to the obligations stated in the signed Statement of the Investigator, Food and Drug Administration (FDA) Form 1572, the regulations governing the rights, safety, and welfare of subjects who are participating in a clinical investigation and the policies for control of investigational drugs. The PI may also act as the IoR when the PI is the physician responsible for the conduct of a specific investigation.

**OHRP:** The Office for Human Research Protections (OHRP) is an office at the Department of Health and Human Services (DHHS) responsible for regulations pertaining to protecting human subjects in biomedical and behavioral Research. The office is located in the Office of the Assistant Secretary for Health. OHRP's functions include implementation of the DHHS Regulations for the Protection of Human Subjects (45 CFR 46), and the provision of guidance on ethical issues in biomedical or behavioral research.

**Pharmacist of Record/Site Pharmacist/Drug Manager:** The Site Pharmacist is the primary individual who is expected to develop and maintain an investigational drug control system, which includes the technical procedures for drug ordering, control, dispensing, and accountability. In addition, the Site Pharmacist may be expected to assist in 1) preparation of blinded study agents, 2) development of special dosage forms and packaging, 3) drug compliance monitoring of subjects, 4) preparation of drug information/data sheets for pharmacy, nursing, and other personnel, 5) data collection and documentation; and 6) development of research protocols.

**Principal Investigator:** The individual responsible for all research activities at the clinical site/center and any affiliated site/center. The PI has the authority to approve or disapprove any new research activities. The PI delegates all clinical and administrative tasks as needed, communicates information and oversees site/center management and staffing concerns. The PI oversees the conduct of each specific protocol or delegates management responsibility for a specific protocol to another physician known as the Investigator of Record (IoR). The PI will

disseminate protocol information to affiliated clinical sites/center; and ensure serious adverse experiences are reported to the Regulatory Operations Center).

**Program Coordinator:** The individual at DAIDS who acts as the liaison between the site/center personnel and the Division of AIDS.

**Quality Assurance:** The process of retrospectively reviewing the various components of the research process to assess the adherence to policy and procedure and determine the accuracy of the entire research record. For example, staff will evaluate key components of source documentation and compare them with completed case report forms. It is a periodic process, for a defined sample, for a defined period.

**Quality Control:** The ongoing, day-to-day process of checking case report forms for logic and completion. For example, are all headers completed? Do the dates match? Are all required areas completed? QC measures do not constitute QA but are a critical piece of the Quality Management Plan. Quality control measures are concurrent, 100percent, and carried out on all samples.

**Quality Management:** The overall process that incorporates both Quality Assurance (QA) and Quality Control (QC) activities into a planned and systematic program that is communicated to all staff, documented, and evaluated for effectiveness.

**Regulatory Operations Center (ROC):** The Regulatory Operations Center manages regulatory responsibilities for DAIDS-sponsored trials. This includes 1) Investigational New Drug Submissions, 2) Site Registration processing and review, 3) receipt and review of Serious Adverse Experience Reports and submission to the Food and Drug Administration, and 4) maintenance of regulatory files.

**Research Clinician:** The Research Clinician (e.g., R.N., N.P., P.A., M.D.) is responsible for directing the care of subjects enrolled in DAIDS-sponsored trials within the context of specific protocol guidelines. This may include but is not limited to 1) interviewing and examining subjects, 2) providing subject care and education about the protocol and matters related to disease course, 3) completing case report forms (CRFs), 4) maintaining subject files, and 5) obtaining follow-up information.

**Source Data:** All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a trial. Source data are contained in source documents (original record or certified copies). Source data include medication histories, medical histories, verification of eligibility, protocol compliance/noncompliance, adverse events/complications, etc.

**Source Document:** Original documents, data, and records where information regarding subjects is "first" recorded. Investigator subject files or hospital records generally are the basis of source document information. The information in the source documents is used to complete the case report forms.

**Source Documentation:** All written and printed source documents that are pertinent to a research subjects' exposure to the investigational agent(s), exposure to other treatments, progress of disease course, and response to therapy. These may include any record of a subject's condition during participation in a research study, including but not limited to the following: hospital charts, clinic notes, X-ray and laboratory reports, consult notes, and letters.

**Study Coordinator/Project Coordinator:** The Study Coordinator is responsible for managing and coordinating the clinical research projects of the clinical site and works closely with the PI and the Research Nurses to ensure proper subject recruitment and protocol implementation. The coordinator establishes and coordinates systems and communication channels between the clinical site and support facilities. The coordinator is the liaison for the investigators, the Data Management Center/Statistical Center, and the Operations Center.

**Co/Sub-Investigators:** In the event that a clinical trial is conducted by a group of clinicians, the PI or the IoR is viewed as the team leader and the associated physicians, physician's assistants, nurse practitioners, and pharmacists are viewed as sub-investigators. All clinicians with prescribing authority should be listed on the FDA Form 1572, box 6.

## **H.9. Contact Information 2000**

DAIDS Clinical Research Management Branch ( CRMB)  
Main Telephone: (301) 496-8214 FAX: 301-480-4582

CRMB Branch Chief - Fred Batzold  
Telephone: (301) 402-0143 Email: fb10c@nih.gov

### **CRMB Staff:**

Adult ACTG Program Coordinator - Margaret (Peg) Rodgers-McKenna  
Telephone: (301) 402-1308 Email: ma16g@nih.gov

Pediatric ACTG Program Coordinator – Karen Reese  
Telephone (301) 496-7124 Email kr54d@nih.gov

CPCRA Program Coordinator - Judith Brooks  
Telephone: (301) 496-7122 Email: jb359r@nih.gov

AIEDRP Program Coordinator – Glenn Sturge  
Telephone (301) 402-1500 Email: gsturge@nih.gov

Clinical Site Monitoring Project Officer - Pamela Scanlan  
Telephone: (301) 496-0701 Email: ps27s@.nih.gov

Financial Management Specialist - John Brooks  
Telephone: (301) 435-3764 Email: jb443w@nih.gov

Program Analyst - Annice Bergeris  
Telephone (301) 402-3221 Email: ab31a@nih.gov

Clinical Program Coordinator - Mieko Meshiro  
Telephone: (301) 402-2307 Email: mm227q@nih.gov

Statistical and Data Management Center (SDAC) Program Coordinator – Peter Gilbert  
Telephone: (301) 402-3224 Email: pg18p@nih.gov

Special Projects and DAIDS CCG Liaison - Margaret Matula  
Telephone (302) 402-2302 Email: mm154j@nih.gov

Special Projects - Karen Oseekey  
Telephone: (301) 402-3222 Email: ko28j@nih.gov

DAIDS Pharmaceutical Affairs Branch (PAB)  
Main Telephone: (301) 496-8213 FAX: (301) 480-5703

For questions about status of drug order, drug supply and product information.  
Telephone: (301) 294-3453 FAX: (301) 294-2905

DAIDS Regulatory Affairs Branch (RAB)

Main Telephone: (301) 435-3741 FAX: (301) 402-1506

Site Registration

Email: [actg.sitereg@fstrf.org](mailto:actg.sitereg@fstrf.org)

Telephone (301)-230-3197 FAX: 800-275-7619

Serious Adverse Experience Reporting Office

Telephone: 1 800-537-9979 FAX 1 800-275-7619